UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and MANULIFE INSURANCE COMPANY (f/k/a INVESTORS PARTNER LIFE INSURANCE COMPANY),	CIVIL ACTION NO. 05-11150-DPW
Plaintiffs,	
v.	
ABBOTT LABORATORIES,	
Defendant.	

AFFIDAVIT OF WILLIAM R. FAIRWEATHER, PhD

Dr. William R. Fairweather, being duly sworn, deposes and says:

Background and Qualifications

1. My name is William R. Fairweather. I reside in Rockville, Maryland.

2. I am a statistician. I was engaged by John Hancock in 2006 to serve as an expert witness in this matter. I have been asked by John Hancock to address for the Court the consequences, from a statistical standpoint, of the facts that: (a) Abbott prematurely terminated enrollment in its Phase IIb clinical trial of ABT-594 (the "M99-114 Trial") short of its original target enrollment of 320; and (b) Abbott experienced an approximately forty-eight percent

(48%) premature termination rate among subjects who actually enrolled in the M99-114 Trial. This affidavit sets forth my direct testimony on these issues.

3. I am being compensated at the rate of $275.00 per hour for my services. My compensation is unrelated to the outcome of this litigation.

4. I have almost 40 years experience as a statistician, including 25 years with the United States Food and Drug Administration (FDA). Since 1999, I have consulted privately to the pharmaceutical industry and to other industries on statistical issues through my firm, Flower Valley Consulting, Inc. A true and accurate copy of my *curriculum vitae* at the time I was engaged is attached to this affidavit as Exhibit A. A brief summary of my educational and employment background is as follows.

5. I obtained a Bachelor of Arts Degree in Mathematics and Statistics from the University of California, Berkeley in 1964. I subsequently obtained a Masters Degree in Statistics from Cornell University in 1966, and a Ph.D. in Biomathematics from the University of Washington, Seattle in 1973.

6. From 1973 to 1998, I was employed by the FDA as a Mathematical Statistician. From 1973 to approximately 1976, I reviewed the statistical aspects of new drug applications submitted by various pharmaceutical companies. I evaluated whether clinical trials were properly designed and analyzed, and whether the sponsoring company drew fair conclusions from the results.

7. In 1976, I was promoted within the FDA to the position of Group Leader of the Statistical Evaluation & Research Branch. I was promoted again in 1979 to the position of Chief of the FDA's Statistical Application & Research Branch. In each position, my duties involved reviewing, and supervising other statisticians who reviewed pharmacokinetics,

biopharmaceutics, animal toxicology, stability, chemistry and manufacturing controls, and post-marketing surveillance studies. I also reviewed new drug applications for proposed treatments for Acquired Immune Deficiency Syndrome (AIDS).

8. From 1996 to 1998, I served as Associate Director of Biostatistics with the FDA. My responsibilities in that position included drafting FDA policies and interpreting FDA standards. I also advised the Office of Biostatistics in statistical methods for evaluating clinical trials and drug safety.

9. Over the course of my 25 years with the FDA, I evaluated the statistical design and claims made by sponsors of literally hundreds of clinical trials. Later in my career with the FDA, I participated in creating guidelines to assist the pharmaceutical industry in understanding and satisfying FDA requirements.

10. While I was employed with the FDA, the FDA declared me to be an "Expert Regulatory Statistician," denoting a high level of experience and expertise. I also received a variety of other awards and forms of official recognition for my work at the FDA, including:

- The Harvey W. Wiley Medal and FDA Commissioner's Special Citation "for outstanding and sustained application of statistical methodology in the areas of post-marketing risk assessment, carcinogenicity, and animal toxicology with the aim of promoting public health" (1999);
- Group Recognition Award for service on the FDA's Carcinogenicity Assessment Committee (1997);
- The Commissioner's Special Citation for Service on the FDA's Tobacco Working Group (1994);

- The United States Public Health Service Special Recognition Award (1987);
- Two FDA Commendable Service Awards (1980, 1983); and
- The FDA's Award of Merit (1976).

11. In 1998, I retired from the FDA and founded Flower Valley Consulting, Inc. As a private consultant, I advise pharmaceutical companies and I participate in the statistical design and analysis of clinical trials, laboratory studies, and animal studies in connection with client efforts to satisfy FDA regulatory requirements. Since founding Flower Valley Consulting, Inc. I have been involved in the design and/or analysis of approximately fifty (50) clinical trials.

12. I also have written several publications on applied statistics and given presentations on statistical and regulatory topics at numerous meetings in the United States, Italy, Israel and Belgium.

Tasks and Summary of Opinion

13. My opinions in this matter are based on documents that I reviewed from Abbott's files, including the protocol for Abbott's Phase IIb clinical trial for the compound known as ABT-594 (the "M99-114 Trial"), as well as various e-mails and other documents relating to the planning and execution of that trial. I also reviewed the deposition testimony of Dr. Bruce Rodda, an expert witness engaged by Abbott, as well as various other depositions of Abbott personnel. My opinions also are based on my experience and on generally-accepted statistical theory and practice.

14. In my opinion, Abbott and its statisticians should have known on or before March 13, 2001, the day the parties entered into the Research Funding Agreement at issue in

this case, that the M99-114 Trial was underpowered and would likely fail to achieve its statistical objectives. Moreover, Abbott should have known that the eventual unblinded results of the M99-114 Trial would be unlikely to move ABT-594 into Phase III trials and, at the very least, probably would delay the commercialization of that compound.

Relevant Statistical Principles

15. From a statistical standpoint, part of the design of a clinical trial is determination of how many subjects must be enrolled. The goal is to enable detection of a statistically significant difference between placebo and the test drug, or between different doses of the test drug. The statistical design of a clinical trial is contained in a written protocol.

16. The number of subjects in a clinical trial is known as the "sample size."

17. Trials are designed to detect an "effect size," for example, the difference between placebo and the test drug.

18. Clinical trials also are designed based on assumptions about "variability," or the range of different responses that subjects may have to a course of treatment. Generally, the greater the anticipated variability, the greater the sample size needed to detect the prespecified effect.

19. "Power" is the probability that a clinical trial will correctly declare a difference between the test drug and placebo when, in fact, there is a difference. Statisticians often plan clinical trials to achieve eighty percent (80%) power for a difference that is considered clinically important.

20. In my experience, pharmaceutical companies do not plan clinical trials to achieve less than 80% power because they desire a high level of confidence that the study will be successful when, in fact, a true difference exists between treatments. Clinical trials are

expensive and unless the trial is planned with sufficient power, the pharmaceutical company may have to repeat it.

21. Moreover, pharmaceutical companies typically plan their clinical trials to maximize the likelihood of FDA approval. Approval is more likely when a company can demonstrate that the effect seen between a test drug and placebo results from the action of the drug, and not by chance alone.

22. In sum, statisticians plan clinical trials by considering the desired effect, anticipated variability, and desired power. They then calculate sample size based on those variables.

23. Generally speaking, reducing the sample size of a clinical trial, when other variables remain constant, reduces the power of the trial.

24. The trial protocol usually also provides the procedures for analyzing data from subjects who enroll in the trial, but terminate prematurely (*i.e.*, cease participating in the trial prior to the scheduled completion of their involvement). Subjects prematurely terminate for many reasons, including adverse events (*i.e.*, an undesirable experience or side-effect). Subjects who prematurely terminate have not provided complete data because they have not completed the trial. Protocols typically provide methodologies for determining how to impute data for subjects that prematurely terminate a trial.

25. As a statistician, I always prefer complete data from each subject. From the FDA's perspective, imputed data is not as reliable or accurate, and can undermine the overall reliability of the clinical trial.

Abbott's M99-114 Trial for ABT-594

26. Abbott's M99-114 Trial for ABT-594 was a Phase IIb clinical trial entitled: "A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy." (Ex. 16, p. i) (Clinical Protocol M99-114 for the Study of ABT-594, dated February 8, 2000 (the "Protocol")). The objectives of the M99-114 Trial were to determine whether, and at what doses, ABT-594 was efficacious and well tolerated. (*Id.* at 9).

27. The M99-114 Trial was designed to "allow for the detection of a 0.46 effect size in [a daily pain intensity] score ... between any ABT-594 treatment group and placebo ... with at least 80% power." (PLs' BY) (E-mail from Abbott statistician regarding goals of trial, dated December 21, 1999).

28. The M99-114 trial provided for a placebo arm and three additional arms dosed twice daily at 150, 225 and 300 mcg respectively. (Ex. 16, Protocol, p. 10). To achieve the desired effect at 80 percent power, Abbott's statisticians determined that the trial required a total of at least 320 patients, or at least 80 subjects in each of the four treatment arms. (*Id.*).

29. The M99-114 protocol also provided a procedure for analyzing data from any subjects that enrolled in the trial, but prematurely terminated. (*Id.* at 42). First, the protocol defined an "intent-to-treat" population, or those subjects that enrolled in the trial and completed at least "1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale." (*Id.* at 40). Second, the protocol provided a methodology called "Last Observation Carried Forward" to impute data to subjects who met the intent-to-treat criteria. (*Id.* at 42) ("The 'last observation carried forward' ("LOCF") analyses will use the completed pain evaluation from the previous visit for site-

based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data").

30. The titration schedule for the M99-114 Trial (*i.e.*, the timetable for increasing dosage to the treatment arms) provided that, on days one through three, all subjects would receive 75 mcg; on days four through five, all subjects would received 150 mcg; on days six through seven, all subjects who were randomized to higher doses would receive 225 mcg; and on day eight, all subjects received the maximum dose to which they were randomized. (*Id.* at 17-18).

31. According to Abbott's Protocol, the M99-114 Trial was scheduled to commence with the enrollment of the first subject in April 2000, and end with the completion of dosing to the last subject in November 2000. (Ex. 16, Protocol, p. ii). Abbott's records indicate that the M99-114 Trial actually commenced on schedule in April 2000. (PLs' EK, p. 7) (ABT-594 Descriptive Memorandum, dated February 2001).

32. Documents that I have reviewed in preparation for my testimony show that by May 2000, or within weeks of commencing enrollment, Abbott was experiencing difficulties enrolling subjects in the M99-114 Trial. (PLs' HJ) (Letter from Abbott stating that "[t]he M99-114 study has its share of enrollment challenges and Abbott appreciates the difficulties some sites have encountered," dated May 25, 2000).

33. By July 2000, subjects were prematurely terminating the trial for, among other things, moderate-to-severe nausea, vomiting and dizziness -- adverse events that Abbott recognized at the time were "typical" of ABT-594. (PLs' CJ) (E-mail from Medical Director of M99-114 Trial stating that "[o]f the 78 subjects enrolled to date, at least 31 have preterm[inated] ... at least 20 appear to have preterm[inated] for AEs typical of our drug

(nausea, vomiting and/or dizziness) ... [a]ppropriately the preterm[ination] rate has created investigator and coordinator reluctance to enroll," dated July 7, 2000). Abbott's documents also disclose its recognition that "many" of the premature terminations were occurring at the titration stage and across all dose levels. (*Id.*) ("[m]any of these subjects dropped in the 3-11 day time frame (the period of dose escalation resulting in 150 mcg BID at day 4, 225 mcg BID at day 6 and 300 mcg BID at day 8)."). Acknowledging the possibility that the adverse events were drug related and to assuage investigator concerns in this area, Abbott considered (but did not) eliminate the 300 mcg dose at this time. (*Id.*).

34. In late August 2000, Abbott extended the enrollment period for its M99-114 Trial until March 2, 2001, in an attempt to compensate for the slow enrollment of subjects in the trial. (PLs' CS) (Letter from Abbott to trial investigators, dated August 31, 2000). Abbott subsequently considered, but rejected, retaining an outside patient recruitment firm to increase enrollment in the M99-114 Trial. (PLs' DH, p. 1) (Abbott November 2000 ABT-594 Project Status Report stating "[p]roposals and timelines from 3 patient recruitment firms were reviewed, with a conclusion reached that hiring a recruitment firm to increase enrollment for study M99-114 was not a viable option at this time.").

35. On January 5, 2001, Abbott terminated further enrollment in the M99-114 Trial more than two months prior to the revised enrollment deadline and short of the official enrollment target of 320 subjects. (Ex. 20, p. 2) (E-mail from Abbott's Clinical Project Manager to trial investigators, dated December 14, 2001, stating "[w]e have decided to end enrollment in the above referenced study [*i.e.*, the M99-114 Trial] on January 5, 2001.").

36. Abbott's final Clinical Study Report for the M99-114 Trial indicates that, as of January 5, 2001, Abbott had enrolled only 266 subjects in the M99-114 Trial. (PLs' FZ,

p. 46) (Clinical Study Report, dated July 31, 2001). Abbott's internal documents further indicate that, on or before March 13, 2001, Abbott was aware that, of the 266 subjects who actually had enrolled in the M99-114 Trial, approximately forty-eight percent (48%) (*i.e.*, 128 subjects) had prematurely terminated, and only approximately fifty-two percent (52%) (*i.e.*, 138 subjects) completed the trial. (*Id.* at ii).

My Conclusions

37. Based on my experience and the materials I have reviewed, I believe that, on or before March 12, 2001, members of Abbott's statistical staff working on the M99-114 Trial were aware, or should have been aware, that the prematurely terminated M99-114 Trial would be underpowered to reach its stated objectives.

38. Specifically, Abbott's failure to enroll the Protocol target of 320 subjects reduced the power for the trial below the planned eighty percent. Only 138 subjects completed the trial. If Abbott reasonably assumed, on or prior to March 12, 2001, that those subjects were distributed relatively evenly across the four treatment arms, with approximately 34 in each arm, Abbott would have recognized that the power of the M99-114 Trial had been reduced to less than fifty percent (50%). (PLs' CQ) (Abbott's power calculations for M99-114, dated August 29, 2000). That is, the probability that the M99-114 trial would declare the test product superior to placebo would be less than the toss of a fair coin.

39. Even in the highly improbable event that *all* of the enrolled patients had been equally divided between the placebo group and just one other group (*i.e.*, the 150 mcg, 225 mcg or 300 mcg arms) thereby resulting in the maximum power possible in the circumstances, Abbott's own power curves indicated that the power of the M99-114 Trial at 69 patients per

group still would have been less than seventy-five percent (75%). (PLs' CQ) (Abbott's power calculations for M99-114, dated August 29, 2000).

40. Based on these facts, I believe that Abbott should have recognized, on or before March 12, 2001, that the likely power for the M99-114 Trial was, in fact, considerably less than seventy-five percent. I also believe that Abbott should have recognized, on or before March 12, 2001, that it probably would have difficulty obtaining a statistically significant treatment effect in the M99-114 Trial and, therefore, that the trial likely would be a failed study.

41. In reaching my conclusions, I have considered that Abbott's Protocol for the M99-114 Trial called for an intent-to-treat analysis for the subjects who prematurely terminated. (Ex. 16, p. 42). However, Abbott should have understood that partial data from premature terminators was far less desirable and reliable than data from subjects who actually completed the trial. In any event, Abbott knew as of March 12, 2001, that only 251 of the 266 enrolled subjects qualified for the intent-to-treat analysis. (*See* PLs' FZ, p. 53); *see also* ¶29 *supra*. If those subjects had been distributed evenly across the four treatment arms, or approximately 62 subjects per arm, the power would have only been approximately 70%. (*See* PLs' CQ)

42. Based on my 25 years of experience at the FDA reviewing results from hundreds of clinical trials, I believe that the FDA would have been unlikely to respond favorably to a Phase IIb clinical trial for a pain drug such as ABT-594 that had experienced a forty-eight percent (48%) drop-out rate among trial subjects, even if a statistically significant drug effect had been observed. In my experience, the FDA would have had serious questions about any statistical conclusions drawn from data that was largely imputed and not observed.

43. It is my opinion that the statisticians at a large pharmaceutical company such as Abbott should have known, on or before March 12, 2001, that ABT-594 would face serious questions from the FDA that might, at the very least, delay or prevent its entry into Phase III clinical trials.

44. I did not see any evidence in the documents that I reviewed indicating that Abbott had another Phase II trial underway in 2000-2001 that would have supported pursuing a Phase III study of ABT-594. To the contrary, it appears that a successful conclusion to the M99-114 Trial (*i.e.*, one demonstrating a statistical efficacy finding that, preferably, was not clouded by a significant number of adverse events) was essential to provide the cumulative scientific evidence that would justify proceeding with a Phase III study of ABT-594.

Signed under the pains and penalties of perjury this 27th day of January, 2008.

/s/ William R. Fairweather
William R. Fairweather, PhD

CERTIFICATE OF SERVICE

I hereby certify that this document is being filed with the Court through the ECF system and that a copy will be sent electronically to counsel for defendant through the ECF system on January 28, 2008.

/s/ Richard C. Abati
Richard C. Abati (BBO No. 651037)

EXHIBIT A

William R. Fairweather, PhD

Flower Valley Consulting, Inc.
15405 Narcissus Way
Rockville MD 20853

1998 to Present

President and Principal in this statistical consulting firm. Responsible for all executive and managerial decisions as well as technical matters. Areas of activity include clinical and preclinical study design and data analysis, methodological research in statistics, and computer program validation. Expert regulatory statistician.

Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)
Rockville MD 20857

1996 to 1998
Associate Director, Office of Epidemiology & Biostatistics

Responsible for drafting policy, interpreting regulations, developing standards. Member of the OEB management team. Also serving as Executive Director for Information Technology for OEB. Principal advisor to the Office, including the Director and Deputy Director, on matters pertaining to research, development, and application of information technology, scientific computing and statistical methods in evaluation of drug chemistry and drug product quality, animal toxicology, drug safety, and clinical trial data quality assurance. Provide scientific leadership. Conduct and coordinate research in statistical methodology, provide expert consultation. Principal, authoritative spokesperson for OEB in these areas of responsibility.

1979 to 1996
Chief, Statistical Application & Research Branch

Provide statistical support to all areas of the Center for Drug Evaluation & Research and (until 1990) the Center for Biologics Evaluation & Research; ie, clinical trial evaluation for safety and efficacy of AIDS and other anti-viral drugs, biologicals, animal tumorigenicity testing, bioequivalence, epidemiology, and compendial standards. Responsible for directing the statistical program, for planning and allocating resources, and for the quantity and quality of work produced by three subordinate units of the Branch (18 professionals, I secretary). Participate in setting of short- and long-range goals for the Division of Biometrics.

1990
Acting Director, Division of Biometrics

Temporary promotion (6 months) while supervisor was overseas. Supervised 2 Branch Chiefs and a Division of over 50 professionals.

1976 to 1979
Group Leader, Statistical Evaluation Branch

First line supervisor of 5 Ph.D. level statisticians and a secretary. Responsible for the quantity and quality of work produced by the Group, which includes approximately 100 technical reports covering clinical trial evaluations for half the prescription drugs approved each year in the U.S.

1973 to 1976
Mathematical Statistician

Perform critical scientific reviews and evaluations of data and statistical methodology submitted by industry in support of New Drug Applications. Develop new methods of statistical analysis, as needed. Present authoritative statistical position of FDA in meetings with medical, legal and statistical personnel from industry.

Electronic Filing Services
Rockville Maryland

1987 to 1997
Partner

Founded this company for electronic filing of Federal and state income tax returns. Responsible for executive decisions regarding company direction, sales and marketing, and computer programming, especially for telecommunications. Firm filed hundreds of electronic tax returns and was profitable each year of its operation.

Biostatistics Department, University of Washington,
Seattle, Washington.

1971 to 1973
Statistical Consultant.

Part time while completing doctorate.

Biometrics Branch, National Heart and Lung Institute,
National Institutes of Health, Bethesda, Maryland.

1968 to 1971
Statistician (Lt., U.S. Public Health Service).

Provide consulting services to intramural laboratory researchers involving design of experiments, data analysis by desk calculator and computer, and interpretation of results.

PhD, Biomathematics, University of Washington, l973
MS, Statistics, Cornell University, l966
AB, Mathematics and Statistics, University of California, Berkeley, l964

Harvey W. Wiley Medal and FDA Commissioner's Special Citation "for outstanding and sustained application of statistical methodology in the areas of postmarketing risk assessment, carcinogenicity, and animal toxicology with the aim of promoting public health." 1999

Group Recognition Award for service on Carcinogenicity Assessment
Committee, 1997
Commissioner's Special Citation for service on Tobacco Working Group, 1994
Commendation for performance as Acting Division Director, 1991
US Public Health Service Special Recognition Award, 1987
Food and Drug Administration Commendable Service Awards, l980 and 1983
Food and Drug Administration Award of Merit, l976
Sigma Xi-RESA, l975
Listed in Who's Who in American Science
U.S. Public Health Service NIH Predoctoral Fellow, University of Washington, l970-l973
John McMullen Graduate Fellow, Cornell University, l964-5
A.B. with Honors, University of California, l964

American Statistical Association
Biometric Society
Federal Executive Institute Alumni Association
Food & Drug Administration Alumni Association

I enjoy a number of activities in addition to my professional work. Among these are martial arts and sailing. I hold a nidan (2nd degree black) belt in aikido and I teach at the Maryland Ki Society.

I am a longtime sailor, and I recently had a new sailboat built in Florida. She is a ComPac 35 sloop. My wife and I plan to sail her in Chesapeake Bay and offshore. Our initial trip, the Round Delmarva 400 Cruising Rally, went very well, so we are now thinking of a trip to New York City or to Rhode Island in the spring of 2005. We are not new to ocean sailing. We joined our son, Brian in Tahiti in July 2000 during his cruise to Tonga.

William R. Fairweather, PHD

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_____ (1996). Regulatory, design and analysis aspects of complex stability studies - A US perspective. Invited paper presented at conference on Stability Testing - Design and Interpretation of Data for International Registration of Pharmaceuticals for Human and Veterinary Use. London, Great Britain.

_____ (1996). Issues in carcinogenicity analyses - An FDA perspective. Invited paper presented at Drug Information Association Workshop on Statistical Methodology in Nonclinical and Toxicological Studies, Brugge Belgium.

_____ (1995). Integrated safety analysis: Statistical issues in the assessment of safety in clinical trials. Paper presented at 31st Annual Drug Information Association meeting. Orlando FL.

_____, D Lin and R Kelly (1995). Regulatory, design and analysis aspects of complex stability studies. J.Pharm.Sci. 84 no 11., 1322-1326.

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Fairweather, WR (1994). TQM in Drug Development. Discussant for three papers at American Statistical Association Winter Meeting, Atlanta GA.

_____ (1994). Design of Stability Studies: FDA Statistical Perspective. Invited paper presented at American Association of Pharmaceutical Scientists Workshop on Stability Guidelines for Testing Pharmaceutical products, Arlington VA.

_____ (1994). Statistical analysis of stability data according to the new requirements. Invited paper presented at conference on Statistical Testing - Design & Interpretation of Data for International Registration of Pharmaceuticals, London, Great Britain. Also presented at Medicines Control Agency, Department of Health, London.

_____ (1994). Statistical Issues of Chemistry and Manufacturing Controls. Discussant for four papers at Joint Meetings of the American Statistical Association, Toronto Canada.

_____ and SD Dubey (1994). Statisticians, the FDA and a time of transition. Keynote address presented at Pharmaceutical Manufacturer's Association Education and Research Institute course in Non-Clinical Statistics, Washington DC.

_____, D Lin and R Kelly (1994). Regulatory and design aspects of complex stability studies. Presented at the Pharmaceutical Research and Manufacturers of America Biostatistics Subsection/Clinical Data Management Group Joint Meeting, Washington DC.

_____ and SD Dubey (1993). Statisticians, the FDA and a time of transition. Keynote address presented at Pharmaceutical Manufacturer's Association Education and Research Institute course in Non-Clinical Statistics, Washington DC.

_____ and RT O'Neill (1993). Training the next generation of biostatisticians - A view from Government. Presented at Joint Meeting of the Biometric Society, ENAR. Philadelphia PA.

_____ (1992). TQM at FDA. Invited paper presented at the national meeting of the American Statistical Association, Boston MA.

_____ and SD Dubey (1992). Statisticians, the FDA and a changing world. Keynote address presented at Pharmaceutical Manufacturer's Association Education and Research Institute course in Non-Clinical Statistics, Washington DC.

_____ (1991). Does "one size fits all" apply to animal carcinogenicity studies? Paper presented at Regulatory Affairs Professional Society meeting on International Toxicology Guidance: Scientific and Regulatory Aspects. Lucca, Italy.

_____ and DJ Schuirmann (1991). Outliers in bioequivalence studies - Should they be included? Paper presented at the Drug Information Association workshop on Bioavailability/ Bioequivalence: Pharmacokinetic and Statistical Considerations. Bethesda MD.

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_____ (1989). Statistical issues in the evaluation of biological growth factors. Paper presented at 25th Annual Drug Information Association meeting. Boston MA.

_____ (1988). Computer-Assisted NDA Review of toxicology and pharmacology data. Paper presented at Joint PMA/FDA-sponsored meeting on CANDAR. Baltimore MD.

_____ (1988). Statistical considerations in tumorigenicity study review. Paper presented at 24th Annual Drug Information Association meeting. Toronto, Canada.

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_____ (1987). Analysis of multiple tumors in carcinogenicity studies. Paper presented at Tenth Annual Midwest Biopharmaceutics Workshop, Muncie IN.

_____ (1987). The future of statistics. Paper presented at Tenth Annual Midwest Biopharmaceutics Workshop, Muncie IN.

_____ (1987). Estimating changes in bioavailability due to generic substitution of drugs. Paper presented at the annual meeting of the American Statistical Association, San Francisce CA.

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_____ and Rastogi SC (1986). General considerations for the review of animal tumorigenicity studies. Paper presented at the annual meeting of the Biostatistics Subsection of the Pharmaceutical Manufacturers Association, Washington, DC.

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Fairweather WR (l985). Current issues in the interpretation of animal tumorigenicity studies. Invited paper (welcoming address) presented at the Symposium on Long-term Animal Carcinogenicity Studies--A Statistical Perspective, Bethesda MD.

_____ (l985). Multiple comparisons in retrospective studies. Paper presented at the Spring Regional Meetings, Biometric Society, Raleigh NC.

_____ (1985). Comparing proportion exposed in case-control studies using several control groups. Paper presented at the International Conference on Foundations of Statistical Inference, Tel Aviv, Israel.

_____ and Harris ND (l985). Performance of Peto's test statistics in simulated tumorigenicity studies. Paper presented at the national meeting of the American Statistical Association, Las Vegas, NV.

Hurwitz, ES, MJ Barrett, D Bregman, WJ Gunn, LB Schonberger, WR Fairweather, et al (1985). Public Health Service study of Reye's syndrome and medications--Report of the pilot phase. New Eng J Med, 313, No.14, 849-857

Fairweather, WR (I984). FDA perspectives in process validation. Invited paper presented at the national meeting of the American Statistical Association, Philadelphia PA.

Krushat, WM, SA Edlavitch, GV Quinnan, Jr., E Barker, WR Fairweather, T Hayes, F Rosa, and DB Burlington (I983). Conditional logistic analysis of the reported association between salicylates and Reye Syndrome. Paper presented (by WM Krushat) to Society for Epidemiological Research, Winnipeg, Canada.

Fairweather, WR (I982). Quality control and statistics at FDA. Paper presented at meeting of the Quality Control Section of Pharmaceutical Manufacturers Association, Arlington, VA

_____ (1982). A model of antibiotic prescribing practices of US physicians: Treatment of URT infections. Paper presented at meeting of the Israel Statistical Association, Jerusalem, Israel.

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EX. 16

ABBOTT LABORATORIES
Clinical Protocol

A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Protocol M99-114

February 8, 2000

Fred Siebert, MT-BB (ASCP)
Senior Clinical Research Associate, Analgesia Venture — 2/10/2000 Date

David Morris, Ph.D.
Manager, Clinical Statistics — 2-11-00 Date

Walid Awni, Ph.D.
Manager, Clinical Pharmacokinetics — 2/11/00 Date

Bruce G. McCarthy, M.D.
Associate Medical Director, Analgesia Venture — 2/10/00 Date

Christopher J. Silber, M.D.
Venture Head, Analgesia Venture — 2/10/00 Date

PLAINTIFF'S EXHIBIT MCCARTHY 68 3/16/07

Abbott Laboratories

1.0 Title Page

Abbott Laboratories
Analgesia Venture, D48Q
Clinical Study

A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

ABT-594/M99-114
February 8, 2000

Development Phase: II

Investigators: Multicenter Trial

Estimated Date of First Subject to be Dosed: April 2000

Estimated Date of Last Subject to Complete Dosing: November 2000

Sponsor/Emergency Contact: Christopher J. Silber, M.D.
Venture Head,
Analgesia Venture
Phone: (847) 938-5236, Fax: (847) 938-5258
Department 48Q, Building AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193

This study will be conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

2.0 Study Synopsis

Name of Company: Abbott Laboratories **Name of Finished Product:** ABT-594 Hard Gelatin Capsule (HGC) **Name of Active Ingredient:** ABT-594	**Individual Study Table Referring to Part of the Dossier:** Not Applicable (N/A) **Volume:** N/A **Page:** N/A	*(For National Authority Use Only)*
Title of Study: A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter Study		
Study Center(s): 30		
Publication (reference): N/A		
Study Period (years): **Estimated Date of First Subject to be Dosed:** April, 2000 **Estimated Date of Last Subject to Complete Dosing:** November, 2000		**Phase of Development:** II
Objectives: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.		
Methodology: This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg, or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll 320 subjects who meet entry criteria for this study. Prior to any study-specific procedures at the Screening Visit, an informed consent will be signed and study eligibility determined.		

Methodology: (Continued)

Prior to study drug administration, subjects will have discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and have completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who meet entry criteria, will be randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Treatment Phase, subjects will return to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). During the Primer and Treatment Phases, subjects will be allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but will not be allowed to take acetaminophen within 24 hours prior to a Treatment Visit). Subjects will complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects will undergo site-based assessments of their neuropathy pain at the Baseline Visit and Treatment Visits I, II, III and IV. Subjects will discontinue study drug administration after Treatment Visit IV and return to the site for the Follow-Up visit 7-10 days later. See Figure 9.1a, Study Schematic, for additional study layout information.

Efficacy and safety assessments will include: the Pain Rating Scale (11-Point Likert), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change.

No. of Subjects: 320

Diagnosis and Main Criteria for Inclusion:

A subject may be randomized in this study provided that he/she meets all of the Inclusion Criteria outlined below and does not meet any of the Exclusion Criteria in Section 9.3.2.

- Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.
- The subject must be age 18 or older and in relatively good health with a recent stable medical history.
- The subject's weight must be ≤ 265 pounds.
- A female subject must be non-lactating and:
  - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),
    OR
  - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

  All female subjects must have a negative β subunit human chorionic gonadotropin (β-hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β-hCG at all Treatment Visits.
- The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam **and** either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.

- The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- The subject must have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) everyday during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

Test Product(s): ABT-594 75 µg HGC (Formulation A-2)

Dose: ABT-594 150 µg, 225 µg, or 300 µg BID (Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
ABT-594 75 µg HGC	58-293-AR

Duration of Treatment: 49 days

Reference Therapy: Placebo for ABT-594 HGC No. 1 Light Gray Opaque (Starch)

Dose: Placebo to match test product (see Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
Placebo for ABT-594 HGC	55-243-AR-01

Criteria for Evaluations:

Efficacy:

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation will be analyzed in a similar manner. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to Day 1 of the study.

Change from baseline to final and each evaluation will be calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36 ™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] PCS, and MCS.

The efficacy evaluations recorded at the Baseline Visit will be used as the baseline score for efficacy evaluations assessed at the investigative site.

Safety:

Safety will be assessed by medical history, physical exam, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.

Pharmacokinetics:

Blood samples for ABT-594 plasma assay will be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who undergo intensive pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max}, and C_{trough} will be determined.

Statistical Methods:

For all safety and efficacy analyses, the primary comparisons will be between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary and site based rating will be analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) will be compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 will be explored, with and without placebo included. Other efficacy analyses will be performed as appropriate.

Treatment emergent adverse events will be summarized by body system and COSTART term and compared using Fisher's exact test.

Statistical Methods: (Continued)

Mean change from baseline to minimum, maximum and final values will be summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits will be flagged in the data listings. Furthermore, laboratory results which satisfy the criteria for limits for statistical analysis will be identified.

To assess dose proportionally and time invariance (from Visit I to Visit IV), dose-normalized C_{trough} and log-transformed dose-normalized AUC, and C_{max} from the subset of subject participating in intensive pharmacokinetic sampling will be subjected to a mixed effects model analysis with effects for dose level, visit, relevant covariates, and perhaps study center. The logarithmic transformation will be employed for AUC and C_{max}. An exploratory analysis will also be performed on the data set obtained from all subjects.

3.0 Table of Contents

Table of Contents (Continued)

Table of Contents (Continued)

Table of Contents (Continued)

4.0 List of Abbreviations and Definitions of Terms

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or A-165594
CSI	Clinical Supplies Invoice
HGC	Hard Gelatin Capsules
IVRS	Interactive Voice Response System
nAChRs	Neuronal nicotinic acetylcholine receptors
NPRO	New Product Research Order
NPS	Neuropathic Pain Scale

5.0 Ethics

5.1 Institutional Review Board or Independent Ethics Committee

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator will obtain a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories will receive documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year. A complete list of documents required prior to initiation of the study is located in Appendix A.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version, Appendix B) and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix C.

5.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and

signed and dated by the subject and the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of an Informed Consent are specified in Appendix D.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study will identify each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the CRFs.

The site will collect information on the subject per International Council on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency should also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site according to the record retention guidelines outlined in Section 12.0.

Neither the subject, the subject's physician, nor the investigator will be informed of the subject's pharmacogenetic results, should they be obtained. If performed, results from individual subjects will be kept confidential and will not be given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples will be stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples will be kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Investigative sites will be selected by Abbott Laboratories. Approximately 30 sites will be selected to enroll subjects for this study.

6.2 Sponsor Information

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form will be generated by Abbott Laboratories. The database for this study will be created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories will be responsible for the statistical analysis of the data.

6.3 Contract Research Organization

Abbott Laboratories will delegate prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to a Contract Research Organization (CRO) for the conduct of this clinical study. The sponsor and CRO will maintain contact in order to manage adequately the progress of the study. The CRO will coordinate and perform all site visits and will prepare trip reports, using the Abbott format, for each visit performed. These reports will detail the activities conducted at all investigative sites and will include all relevant observations. All trip reports will be forwarded to the sponsor in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures (SOP).

6.4 Clinical Supply Management

Clinical supplies will be prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories will authorize the release of clinical supplies once the appropriate essential documents have been received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

All subjects will be centrally randomized by site and assigned to a treatment group (using a randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS will be contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using a randomization supplied by Abbott Laboratories) will also be assigned using IVRS. Each site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records (Appendix E), and records for return of used and unused clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) will check drug accountability records regularly.

6.5 Central Laboratory

This study will utilize one central laboratory contracted by, and under the direction of, Abbott Laboratories. All protocol specified clinical laboratory tests will be performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

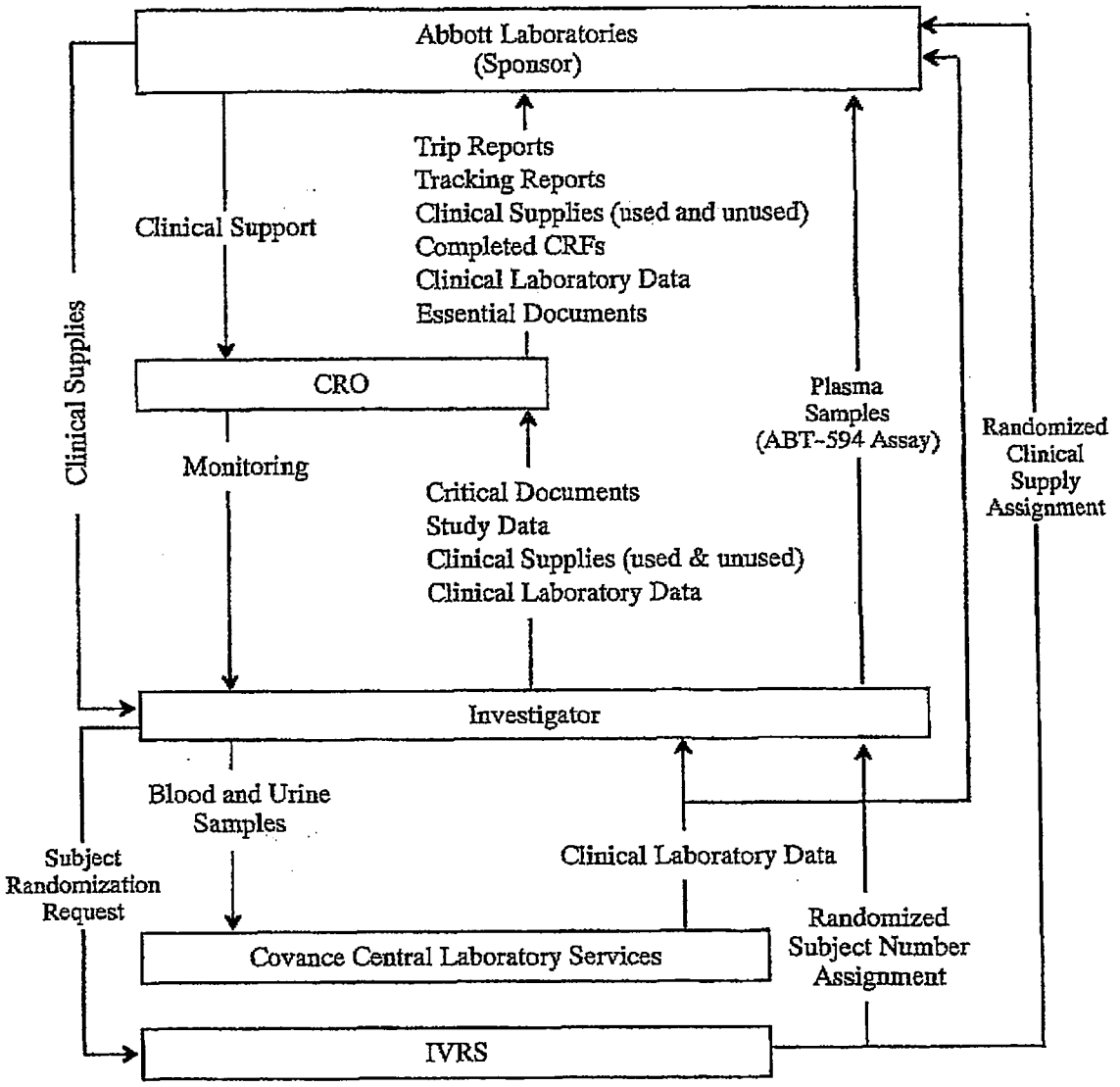

Figure 6.6a Administrative Structure

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.[1]

Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (±)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.[2] The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that

acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.[3] Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

Human clinical trials with ABT-594 began in 1997. Initial clinical trials were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 μg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Two Phase I studies with the HGC formulation have recently been completed: Study M99-076 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Ascending Doses of Twice Daily Dosing Regimens of a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects") and M99-120 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability and Pharmacokinetics of Escalating Doses of Twice Daily Dosing of a Hard Gelatin Capsule Formulation of ABT-594 in Adult Subjects in General Good Health"). Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 μg BID for 14 days. Study M99-120 included titrated doses up through 450 μg BID for 5 days. Adverse events, significantly different than placebo, for subjects receiving 300 μg BID for 14 days in Study M99-076 included: dizziness , nausea, vomiting, asthenia and diarrhea (all of which were considered to be mild in the opinion of the investigator). In addition, results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

Phase II has included (to date) efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon a study of molar extraction pain (Study M97-772, "A Randomized, Double-Blind, Single Dose Comparison of an Oral Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental Pain Model"), 100 μg ABT-594 (single dose oral solution) appeared to be a minimally efficacious dose in acute pain.

A study of ABT-594 in osteoarthritis (Study M98-826, "A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain Associated with Osteoarthritis of the Knee") evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 μg BID for 3 weeks and a study of ABT-594 in neuropathic pain (Study M98-833, "A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Patients with Painful Polyneuropathies") evaluated the same formulation at doses of 25 and 75 μg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 μg BID. In addition, 75 μg BID was generally well tolerated. The most common adverse events (greater than or equal to 5%) for subjects receiving 75 μg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature terminations).

Data from Phase I and II studies completed to date suggest that ABT-594 will be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 μg BID). In addition, data from Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 μg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, will be performed to test this hypothesis.

8.0 Study Objectives

The objective of this study is to compare the safety and analgesic efficacy of 150 μg, 225 μg, and 300 μg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 μg, 225 μg, 300 μg or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll approximately 320 subjects who meet entry criteria for this study.

The study will be divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 is the first day of study drug administration. Subjects will be allowed a window of ± 3 days for each study visit. The study design is depicted in Figure 9.1a.

Subjects will review and sign the informed consent prior to the conduct of any study specific procedures. Subjects will then be screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclics, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs (AEDs), or other analgesics for the treatment of their pain must have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase (Day -7 to Day -1). During the Baseline Pain Assessment Phase, subjects will complete, at approximately 11 AM each morning, the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity. Subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7) during the Baseline Pain Assessment Phase.

On the day after the Baseline Pain Assessment Phase, subjects will return to the site for their Baseline Visit (Day 1). At this visit, diaries will be collected and reviewed. In addition, subjects will complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who meet all entry criteria, including an average of ≥ 4 points on the

diary-based Pain Rating Scale (11-Point Likert) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, will then complete the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects will undergo an interim medical history, physical examination, vital sign measurements, ECG and clinical laboratory tests.

Subjects who meet all entry criteria at the Baseline Visit will be randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 μg BID, ABT-594 225 μg BID, ABT-594 300 μg BID, or placebo. Subjects will start study drug at the evening dose on Day 1 (as specified in Section 9.4.5). During the Primer Phase, subjects randomized to ABT-594 will receive a fixed dose escalation of ABT-594 (as specified in Section 9.4.1). Following the Primer Phase, subjects will enter the Treatment Phase (Day 8) and will continue their treatment for a total of 49 days. During the Primer and Treatment Phases, subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7)

Subjects will complete the diary-based Pain Rating Scale each morning (approximately 11 AM), 3 hours after taking their morning dose of study drug. They will return to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV will include collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III) and efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute) (Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements and clinical laboratory tests (Treatment Visits I, III and IV), ABT-594 plasma assay collection (Treatment Visits I and IV only) and ECG (Treatment Visit IV only). A subset of subjects at selected sites will undergo intensive pharmacokinetic sampling at Treatment Visits I and IV.

On the day after Treatment Visit IV, subjects will enter the Post-Treatment Phase. Subjects will no longer take study drug or complete pain scales. Subjects may restart all discontinued medications under the guidance of their physician. Subjects will return for study procedures at the Follow-up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-up Visit will include physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participate in clinical studies of ABT-594 and who consent, a blood sample will be collected at Treatment Visit I in order to obtain a sample of genetic material (DNA). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

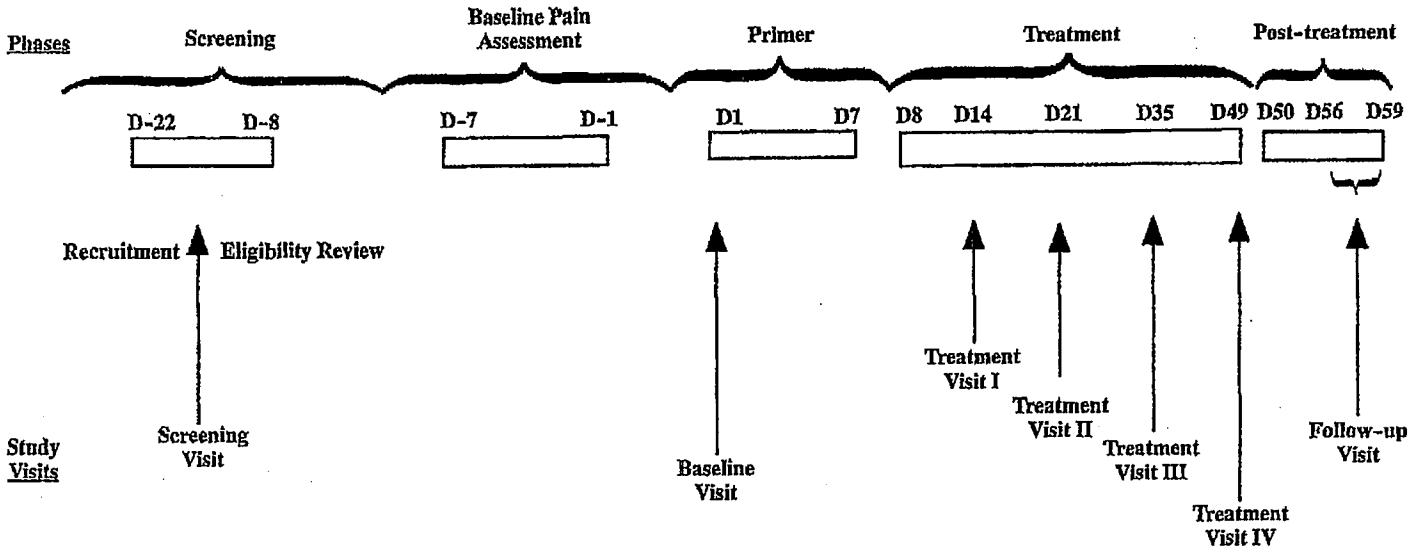

Figure 9.1a Study Schematic

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provides a placebo control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales will be employed.

9.3 Selection of Study Population

It is anticipated that approximately 320 subjects will be randomized and receive study medication in this study. A subject may be randomized in this study provided that he/she meets all of the inclusion criteria outlined in Section 9.3.1 and does not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

9.3.1.1 Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.

9.3.1.2 The subject must be age 18 or older and in relatively good health with a recent stable medical history.

9.3.1.3 The subject's weight must be ≤ 265 pounds.

9.3.1.4 A female subject must be non-lactating and:

- of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),

  OR

- of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative β subunit human chorionic gonadotropin (β-hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β-hCG at all Treatment Visits.

9.3.1.5 The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.

9.3.1.6 The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam **and** either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.

9.3.1.7 The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.

9.3.1.8 The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).

9.3.1.9 The subject must have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

9.3.2.1 The subject has positive test results for drugs of abuse or viral hepatitis at the Screening Visit, or has a known history of a positive test result for HIV.

9.3.2.2 The subject has recent (< 5 years) history of drug or alcohol abuse or dependence.

9.3.2.3 The subject has an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.

9.3.2.4 The subject has active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that has been treated or other malignancies that have been surgically removed and have had no evidence of recurrence for a minimum of 5 years prior to study start).

9.3.2.5 The subject has taken an investigational drug within 1 month prior to administration of study treatment or is scheduled to receive an investigational drug other than ABT-594 during the course of this study.

9.3.2.6 The subject has a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.

9.3.2.7 The subject has orthostatic hypotension at the Screening Visit (as defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing), or a history of syncope or pre-syncopal symptoms.

9.3.2.8 The subject has previously participated in a study involving ABT-594, including the present study.

9.3.2.9 The subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including AST or ALT $\geq$ 1.5 times the upper limit of the reference range or a serum creatinine > 1.5 mg/dL. Subjects may have elevated serum and urine glucose, but their serum glucose must have been under good control (in the opinion of the investigator) for at least the last 3 months prior to the Screening visit.

9.3.2.10 The subject has clinically significant electrocardiographic abnormalities.

9.3.2.11 The subject has ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.

9.3.2.12 The subject has a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject cannot differentiate from the neuropathy pain.

9.3.2.13 The subject has sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.

9.3.2.14 The subject is unlikely to comply with the study protocol or is unsuitable for any other reason, in the opinion of the investigator.

9.3.3 Removal of Subjects from Therapy

A subject may voluntarily terminate participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to

terminate prematurely a subject's participation. The investigator must notify the CRA within 24 hours and document the reason for premature termination on the appropriate CRF.

Subjects, whose participation is terminated prematurely after signing study consent but before study drug administration, will not require follow-up observations. Subjects, whose participation is terminated prematurely after study drug administration must undergo procedures normally performed at Treatment Visit IV (see Table 9.5a) within 7-10 days following termination from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represents a significant risk to subjects, the study will be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID
ABT-594 225 µg BID
ABT-594 300 µg BID
Placebo for ABT-594 BID

ABT-594 and matching placebo will be supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects will receive a fixed dose escalation of ABT-594. ABT-594 will be initiated at 75 µg BID. The dose will increase every 2 days in 75 µg BID increments until subject are taking their assigned treatment dose (150, 225 or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4.1a.

Table 9.4.1a ABT-594 Dose Escalation

Treatment Regimen	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

Subjects will start study drug at PM dose on Day 1 (Section 9.4.5).

The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4.1b.

Table 9.4.1b Number and Type of Capsules by Treatment Regimen

Treatment Regimen	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg	2	2
ABT-594 225 µg	3	1
ABT-594 300 µg	4	0
Placebo	0	4

9.4.2 Identity of Investigational Products

Table 9.4.2a Identity of Investigational Products

Test Preparation Drug Product	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR	52-015-KD-00	Abbott[1]
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	N/A	Abbott[1]

[1] Pilot Plant, North Chicago, Illinois

ABT-594 75 µg HGC and placebo HGC are identical in appearance, encapsulated in Light Gray Opaque capsule size No. 1 HGCs.

9.4.2.1 Packaging and Labeling

Study drug supplies will be blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards will be provided to each subject.

Daily study medication cards will be labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space will be provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies must be stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies must be stored at controlled room temperature (68-77°F, see USP).

9.4.2.3 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. Study drug will be dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who meets the enrollment criteria. The investigator or designee will record the subject number, subject initials and date dispensed to the subject on the Drug Accountability Form (Appendix E). The amount of study drug remaining will be recorded at Visits I, II, III and IV for each subject on the site Drug Accountability Form. An accurate running inventory of study drug will be kept and will include the NPRO number, CSI number(s), the number of modules dispensed and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for and returned to Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with the instructions of the CRA, will also be included in the shipment. The investigator agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects will be centrally randomized by investigative site using an Interactive Voice Response System (IVRS). Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site.

Approximately 320 subjects will be randomized in an equal ratio to receive either ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID or placebo. Subjects will be assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects will start study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects will then take BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs should be taken with at least one cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject will remain blinded to the subject's treatment throughout the course of the study. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) MUST be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. Blind breaking information will be provided using IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site. The sponsor must then be notified within 48 hours of the blind being broken. The date, and reason for blind breakage must be recorded on the appropriate CRF.

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks will be taken.

Concomitant analgesics (prescription or over-the-counter [OTC] except aspirin and acetaminophen as described below), including serotonin-specific reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, muscle relaxants, TENS and topical analgesics will not be allowed.

Aspirin, 325 mg daily maximum, is permitted if taken for primary prevention of thromboembolic events and the dose has been stable for $\geq$ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, is permitted. Subjects will not be allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline Visit and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication is necessary during the course of this study, the medication name, dosage information, frequency and dates of administration must be reported on the CRF. Concomitant analgesic medication use (frequency only) will be recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and Treatment Visits I, II, III and IV. The concomitant medication use record will include the number of separate occasions each subject has used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects will be instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance will be documented by the investigator or designee on the site Drug Accountability Form (Appendix E) and on the appropriate CRF.

Overdose information will be collected on the appropriate CRF.

9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures

9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Study procedures will be performed as summarized in Table 9.5a., Study Procedures Flow Chart.

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7		Treatment Phase D8-D49					Post-Treatment Phase D50-D59	
						Treatment Visit					
	Screening Visit		Baseline Visit D1	D2-D7	D8-D49	D14 I	D21 II	D35 III	D49 IV[a]		Follow-up Visit D56 to D59
Informed Consent	X										
Medical History	X		X[b]						X		
Physical Exam	X[c]		X						X		X
Vital Signs	X[d]		X[e]			X		X	X		X
ECG			X						X		X[f]
Clinical Laboratory Tests[g]	X		X			X		X	X		X[f]
Viral Hepatitis Screen	X										
Urine Drug and Alcohol Screen	X										
Pregnancy Test			X			X[h]	X[h]	X[h]	X[h]		
Genetic Polymorphism Sample (If Applicable)			X								
ABT-594 Plasma Assay						X			X		
ABT-594 PK Profile[i]						X			X		
Diary Issued	X		X			X	X	X			
Diary Collected			X			X	X	X	X		
Diary-Based Pain Rating Scale[j]		X		X	X						
Site-Based Pain Rating Scale			X			X	X	X	X		
Neuropathic Pain Scale			X			X	X	X	X		
Subject/Clinician Global Impression of Change									X		
SF-36™			X						X		
Randomize Patient			X								
Dispense Study Drug			X			X[k]	X	X			
Analgesic Use Monitoring			X			X	X	X	X		
Adverse Event Monitoring			X			X	X	X	X		X
Concomitant Medication Monitoring			X			X	X	X	X		X
Study Drug Accountability		X				X	X	X	X		

a Or upon premature termination.
b Interim history.
c Includes height.
d Includes orthostatic measurements at Screening Visit only.
e Includes oral temperature at Baseline Visit only.
f Performed only if there are clinically significant abnormalities at the previous evaluation.
g Chemistry, hematology and urinalysis.
h Required of all females of child-bearing potential.
i Study drug must be taken in front of study staff. Blood samples from selected subjects will be taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.
j To be completed at approximately 11 a.m., each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.
k Redispense D15–20 study medication after checking drug accountability.

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer will instruct the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) will be the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments include the diary-based and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale and the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements should be performed (when possible) 3-4 hours post dose.

Pain Rating Scale (11-Point Likert Scale)

Subjects will assess pain intensity daily by completing the Pain Rating Scale (Appendix F) in their diaries. These assessments will be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects will record the time they completed these assessments in their diaries.

Subjects will also assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments will be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature termination). The time of assessment will be recorded on the appropriate CRF.

Neuropathic Pain Scale

The Neuropathic Pain Scale (Appendix G) will be completed by subjects at the Baseline Visit and at Visits I, II, III, and IV (or upon premature termination).

Subject Global Impression of Change

The Subject Global Impression of Change (Appendix H) of analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

Clinician Global Impression of Change

The Clinician Global Impression of Change (Appendix H) of a subject's analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) will be completed by each subject at the Baseline Visit and at Treatment IV (or upon premature termination).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

Medical History

A complete medical history will be obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening will be recorded. The medical history will be updated at the Baseline Visit.

Physical Examination

A physical examination, including weight, will be performed at the Screening Visit, Baseline Visit, Treatment Visit IV and at the Follow-up Visit. Height will be measured at the Baseline Visit only. The physical examination performed at the Baseline Visit will serve as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate will be measured at the Screening Visit, Baseline Visit, Visits I, III, and IV and at the Follow-up Visit. Orthostatic blood pressure and pulse rate will be measured at the Screening Visit only. Oral temperature will be taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit will serve as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) should be obtained after the subject has been sitting for at least 3 minutes. Orthostatic measurements should be obtained after 3 minutes in the supine position and then after 1 minute in the standing position. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Subjects should not wear tight sleeves. Ideally, the subject's blood pressure should be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws. Subjects should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

Electrocardiogram (ECG)

A resting 12-lead ECG will be obtained at the Baseline Visit and Treatment Visit IV. An ECG will be performed at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The ECG performed at the Baseline Visit will serve as the baseline ECG.

A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples will be obtained for the laboratory tests listed in Table 9.5.b at the Screening Visit, Baseline Visit (Day 1), and Treatment Visits I, III, and IV. Laboratory tests will be obtained at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The laboratory test results obtained at the Baseline Visit will serve as the baseline results. Blood draws should be performed after pain assessments or vital sign determinations during a visit.

Table 9.5b Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total bilirubin	pH
White Blood Cell (WBC) count	Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)	Bilirubin
Neutrophils	Aspartate aminotransferase/serum glutamic-oxaloacetic transminase (AST/SGOT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Hemoglobin A_{1c} (Baseline Visit Only)	Chloride	
Lymphocytes	Calcium	
Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)	Inorganic phosphorus	
Platelet count (estimate not acceptable)	Uric Acid	
Prothrombin Time (PT)	Bicarbonate	
Partial Thromboplastin Time (PTT)	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

The investigator will review all laboratory test results and will assess clinical significance for each abnormal result. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A copy of each laboratory report must be included with the CRF.

Viral Hepatitis Screen

Subjects will undergo serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody) at the Screening Visit. The hepatitis test panel will be performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens will be tested for drugs of abuse and alcohol at the Screening Visit and will be performed by the central laboratory.

Pregnancy Test

A urine pregnancy test will be performed by designated study personnel at the Baseline Visit for all female subjects and at Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female will not be eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected and unfavorable event such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of a drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject.

The subject will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken and all adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be reported on the appropriate CRF.

The investigator will assess and record any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known), severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

Table 9.5c Definitions for Investigator Rating of Adverse Event Severity

Rating	Definition
Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Rating	Definition
Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

Adverse events will be monitored continuously from the time of study drug administration to the Follow-up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature termination) will be collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects will be instructed to report to the investigator any other adverse events that occur after Follow-up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures that occur after signing the Informed Consent and prior to the first dose of study drug will also be collected.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

Ongoing medical conditions will be considered adverse events if there is an increase in severity or frequency of occurrence. Since measurements of pain intensity are efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study will not be considered adverse events for the purposes of this study.

Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to Abbott Laboratories as a serious adverse event (SAE) within 24 hours of occurrence or notification to the site:

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).

Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions will be reported to Abbott Laboratories as serious adverse events.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone, one of the following people at Abbott Laboratories within 24 hours of being made aware of any serious adverse event.

Bruce G. McCarthy, M.D.
Associate Medical Director
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193
Office: (847) 935-6244
Home: (773) 529-5729
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In addition, a written confirmation of the occurrence, including any supplementary data, must be sent within 3 days of the telephone report to:

Bruce G. McCarthy, M.D.
Dept. 48Q, Bldg. AP34
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-6193
Fax: (847) 938-5258

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study are validated and are considered standard for this population. All clinical and laboratory procedures in this study are standard and generally accepted.

9.5.3 Efficacy Variables

All efficacy variables will be derived from the efficacy measurements (Section 9.5.1.1).

9.5.3.1 Primary Variable(s)

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variable(s)

Change from baseline to final and each scheduled evaluation will be calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert), change from baseline to each evaluation only
- Site Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health][4] PCS, and MCS.[5]

The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site.

9.5.4 Drug Concentration Measurements

9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay

Blood samples for ABT-594 plasma assay will be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) will be collected into a sodium heparin evacuated collection tube at each visit. Blood draws should be

performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinue, a blood sample will be taken for ABT-594 assay at the premature discontinuation visit, and the exact times at which the dose was taken will be recorded.

All blood samples will be immediately stored at 4°C or below. The samples will be separated by centrifugation within one hour after sample collection. The supernatant will be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information will also be recorded on the appropriate CRF. All labeled plastic vials will be placed in a rack to prevent breakage. **Plasma samples for determination of ABT-594 must be frozen at -5°C or colder within one hour from centrifugation.** All specimens will be kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the day of plasma assay blood draw, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draw will be recorded in the CRF.

9.5.4.2 Additional Pharmacokinetic Sampling

For those subjects participating in the additional pharmacokinetic sampling for PK profile (approximately 30 subjects), blood samples will be collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject will be instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication will be taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit should accommodate a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples will be collected as follows: just prior to dosing (0 hour)

and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects will receive their 8 PM dose as scheduled. Subjects will be confined at the site until the blood sample at the 8 hour time point is collected. Pharmacokinetic profile samples will be processed and stored as specified in Section 9.5.4.1 until shipment to Abbott Laboratories.

9.5.4.3 Shipment of Plasma Samples

An inventory list of the samples included in the shipment must accompany the shipment. The inventory list will include the shipping date, number of samples in the container, drug identification, Abbott protocol number, subject numbers, sample type, sampling times, and missing samples. The frozen samples will be packed in dry ice sufficient to last 2 days during shipping.

Arrangements will be made with Abbott Laboratories for shipping of the plasma samples to the following Abbott address:

Sample Receiving
Abbott Laboratories
Dept. 4TA, Bldg. AP9
100 Abbott Park Road
Abbott Park, IL 60064-6122
Phone: (847) 937-0889
Fax: (847) 938-9898

On the day of shipping, a copy of the inventory sheet should be faxed to the Sample Receiving Department at (847) 938-9898.

9.5.5 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples will be collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to

ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis will not be reported with the study summary. The samples may also be used for development of a diagnostic test for drug response.

The pharmacogenetic analyses involve two methods: one which examines known genes believed to be involved in the particular response (Candidate Gene), and one which uses a high density marker map to locate and identify genes related to the response (Genomic Association) by comparing the marker profile between the subjects with an effect and a corresponding negative control group. The Candidate Gene method includes genes related to drug metabolism, drug targets or target pathways, and others including genes relating to cellular homeostasis. The Genomic Association method utilizes a map of single nucleotide polymorphisms which by themselves are essentially meaningless, but when correlated with groups of two distinct subject groups allow the identification of the gene(s) related to the difference between the groups. For the purpose of pharmacogenetic studies such as this, the difference would be related to the response to the drug or the presence or absence of the disease being tested.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting will entail a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and be given a CRF completion workbook for reference. The CRAs will monitor each site approximately every 4 weeks. At each visit, 100% source-document review will be made against the entries on the CRFs and a quality-assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. The investigator must agree to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

The SF-36™ Health Status Survey (Acute) will be recorded directly on the CRF and will be considered source data.

All CRFs must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the CRFs for completeness and accuracy and sign and date the set of case report forms where indicated.

Each CRF will be printed on 3-part NCR paper. The forms consist of a white, yellow and pink copy. The white and yellow copy of the completed, verified CRF will be collected by the CRA and the pink copy retained at the investigative site.

Data captured on the CRF will be entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF will be reviewed and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values, and any necessary corrections will be made to the database and documented via addenda or audit trail.

The laboratory results will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests will be 2-tailed and considered statistically significant if the P-value (Type 1 error rate) is less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons will be made as considered necessary. No statistical adjustments will be made for multiple comparisons.

The baseline for all variables (except for the diary-based Pain Rating Scale) will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses will be performed for 2 sets of data: intent-to-treat subjects and evaluable subjects. Subjects receiving at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert) will be included in the intent-to-treat analyses. The evaluable dataset will include subjects that receive at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses will be performed with all randomized subjects who receive at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements will be assessed. The analyses will be performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to r x c tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation will be calculated for all efficacy variables (except both Global Impression of Change scores).

Primary Efficacy Analysis

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable will be evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment group by study center interaction. If the interaction term is not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences will be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers have fewer than 1 subject per treatment group in the intent-to-treat dataset, data from such centers will be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert) score will be assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change will be analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS may also be analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation will be assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert). For the diary-based Pain Rating Scale (11-Point Likert), change from baseline to each scheduled evaluation will be analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change will be evaluated using CMH methodology on actual scores.

If indicated, exploratory analyses will be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

Dose response for ABT-594 will be explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites is not significant, then the nonparametric Jonckheere-Terpstra test will be used instead of Page's test to assess dose response of ABT-594.

Other analyses will be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, will be performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses will use the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis will have data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely terminate for lack of efficacy. The "observed cases" (OC) analysis will not estimate the missing evaluation, and a subject who does not have pain evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item will be calculated, when less than one-half (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

9.7.1.4 Safety Analyses

All subjects receiving at least 1 dose of study drug will be evaluated for safety.

Adverse events will be coded using the COSTART V[6] dictionary. Treatment-emergent adverse events (i.e., those which begin or worsen in severity after randomized study drug is taken) will be tabulated by body system and COSTART term for each treatment group. Treatment group differences will be evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, will be presented for each treatment group. Analyses by subgroup will be performed as appropriate.

Laboratory data will be analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses will be on the change from baseline to the minimum, maximum and final values during the study for each laboratory variable.

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) will be summarized.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory results which satisfy the criteria for limits for statistical analysis (Appendix I) will be identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG will be analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfy the criteria for below and above limits (Appendix I) will be identified.

Concurrent medication use will be summarized by treatment group.

Additional safety analyses will be performed as indicated.

9.7.2 Determination of Sample Size

The study is designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation is based on results obtained from Study M98-833 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy[7] and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

9.7.3 Pharmacokinetics/Pharmacodynamics

The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the trough plasma concentration (C_{trough}) will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) will be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{max}, dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{max} from the subset of subjects participating in the additional pharmacokinetic (PK) sampling will be subjected to a mixed effects model analysis. The model will include dose, visit (Visit I and Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine use status, and other variables that might account for variability in pharmacokinetics will be included as covariates. The study center factor will be included in the initial model, including a center main effect and, as appropriate, interaction of center with other factors. The center factor, or at least the interaction terms involving center, may be dropped from the model if they explain little of the variability in the data. If the number of subjects who have only Visit I data and not Visit IV data exceeds 20% of the subjects with intensive PK sampling, then analyses will also be performed for each visit separately. The hypothesis of invariance with dose will be tested by comparing the 300 µg BID dose vs the 150 µg BID dose. If the hypothesis of dose proportionality is rejected in a comparison, then the

225 µg BID dose will be compared to each of the 150 and 300 µg BID doses. If the visit by dose interaction is statistically significant, then a comparison will be made for each visit.

An exploratory analysis will also be performed on the data set obtained from all subjects (including those who do not participate in the intensive PK sampling). This analysis will appropriately take into account the time of sampling relative to dosing. The questions of dose proportionality and change from Visit I to Visit IV will be considered in this analysis.

If there is some evidence from the data of this study that ABT-594 is efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable will be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration will utilize the data of all subjects. An analysis using only the data of subjects undergoing intensive PK sampling may also be done. The model will include effects for efficacy variable baseline value and for visit. The center factor will be incorporated appropriately. The dependency of the measurements from the same subject will be accounted for.

Other analyses may be performed as necessary.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

This study will be conducted in accordance with the protocol, GCP, all applicable local, state federal regulations and regulatory requirements. Neither the investigator nor the CRO will modify this protocol without first obtaining the concurrence of Abbott Laboratories. The modification must be documented in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the subject or those of an administrative or clarifying nature, must be reviewed and approved by the Institutional Review Board before implementation. Abbott Laboratories must submit protocol amendments to the FDA and possibly to other government agencies.

This study will be terminated if these conditions are not met.

10.0 Protocol Deviations

When deviation from the protocol is deemed necessary for an individual subject, the investigator or other physician in attendance must contact the site study monitor at the CRO, who will contact Abbott Laboratories. Such contact will be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. Any departures from the protocol will be authorized only for that one subject. A description of the departure from the protocol and the reason for it will be recorded on the CRF.

11.0 Use of Information and Publication

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 90 days before the date of submission to the intended publisher.

Neither the subject nor their physician will be informed of individual subject pharmacogenetic results, should they be performed, nor will anyone not directly involved in this research. This is due to the fact that, 1) the subject and their physician are already

aware of the subject's particular response to the drug and the study information would not affect their future medical care, and 2) if an association is established between a genetic sequence and a treatment response, separate studies must be conducted in order to validate or confirm the results and the properties of the test prior to the necessary regulatory approval to use the test for diagnostic purposes. DNA samples from this protocol may be used either for gene identification, validation, or diagnostic test development studies, as well as discovery of genes related to painful diabetic polyneuropathy.

12.0 Completion of The Study

The investigator will complete and report this study in satisfactory compliance with the protocol within 9 months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon in writing by both the investigator and Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are not pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (printed or typed)

14.0 References

1. American Academy of Pain Medicine (1997). The Use of Opioids for the Treatment of Chronic Pain. pp. 1–4.

2. **Sullivan JP and Bannon AW.** Epibatidine: pharmacologic properties of a novel nicotinic acetylcholine agonist and analgesic agent. *CNS Drug Rev.* 2(1):21-39, 1996.

3. **Sullivan JP, Briggs CA, Donnelly-Roberts D, Brioni JD, Radek RJ, McKenna DG, Campbell JE, Arneric SP, Decker MW, Bannon AW.** (±)-Epibatidine can differentially evoke responses mediated by putative subtypes of nicotinic acetylcholine receptors (nAChRs). *Med Chem Res*, 4:502-516; 1994.

4. **Ware JE.** SF-36™ Health Survey Manual and Interpretation Guide. The Health Institute, New England Medical Center, 1997.

5. **Ware JE.** SF-36™ Physical & Mental Health Summary Scales: A User's Manual. Health Assessment Lab, New England Medical Center, 1994.

6. "COSTART" Coding Symbols for Thesaurus of Adverse Reaction Terms: Fifth Edition, Department of Health and Human Services, Food and Drug Administration, Rockville, MD, 1995.

7. **Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E.** Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. **JAMA.** 208(21):1831-1836, 1998.

Appendix A

Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott Laboratories has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed protocol for the study.
2. A signed Form FDA 1572 or equivalent document certifying the investigator's agreement to comply with U.S. Federal (21 CFR, ICH GCP Guidelines) regulations governing the conduct of the study.
3. A signed Abbott Financial Disclosure form.
4. A current curriculum vitae of the investigator. If sub-investigators will participate in the study, a curriculum vitae for each.
5. Requirements for the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
   - A copy of the letter of approval of the IRB/IEC. The letter must specify that both the protocol and consent form were approved.
   - The names and affiliations of the members of the IRB/IEC or assurance number.
   - If the principal and/or sub-investigator is a member of the IRB/IEC, a letter stating that he/she did not participate in the review or approval of the protocol or consent form.
6. A specimen copy of the IRB/IEC-approved informed consent document to be used in the study.
7. A list of normal ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
8. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

As a rule, these documents will be provided in the course of one or more visits to the investigator by an Abbott Laboratories representative. Usually the study cannot begin until all of the documents listed above have been provided.

Appendix B
Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,
35th World Medical Assembly, Venice, Italy, in October 1983,
41st World Medical Assembly, Hong Kong, in September 1989 and
48th General Assembly, Somerset West, Republic of South Africa 1996.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Appendix B (Cont.)

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

Appendix B (Cont.)

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obligated to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

Appendix B (Cont.)

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician - patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REASON FOR REVISION: Revised to correspond to the amendment adopted by the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa 1996.

Appendix C
Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott Laboratories are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is actually a form letter addressed to the sponsor (Abbott Laboratories), summarizing the investigators qualifications for the study and their willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. To secure prior approval of the study by an appropriate institutional review board which conforms to FDA regulations.
2. To make at least yearly reports on the progress of the study to the above committee, and a final report within three months of study completion.
3. To maintain current running records of the receipt, administration, and disposition of study medication and to return all unused study medication to Abbott Laboratories.
4. To obtain valid written informed consent from each patient who participates in the study.
5. To prepare and maintain adequate case histories of all persons entered into the study, including case report forms, hospital records, laboratory results, etc., and to maintain these data for a minimum of two years following notification by Abbott Laboratories that all investigations have been discontinued with this drug.
6. To identify all subinvestigators who will also supervise drug administration.
7. To report adverse effects to Abbott Laboratories promptly. In the event of serious or unexpected adverse event, to notify Abbott Laboratories immediately by telephone.
8. To allow possible inspection and copying by the FDA of case reports and records of drug distribution.

Appendix D
Elements of the Consent Form

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

For IND Studies, procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all patients participating in PPD Clinical Research studies or the patients' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of patients involved in the trial.
4. The expected duration of the patient's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The patient's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the patient and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the patient for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the patient, this should be stated.

Appendix D (Cont.)

13. The anticipated prorated payment, if any, to the patient for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
15. A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research patient's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the patient.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the patients' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the patient or the patient's legally acceptable representative is authorizing such access.
21. A statement that the site will collect information on the patient per ICH requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency will also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site.
22. A statement that the records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the patients' participation in the trial may be terminated.

Appendix D (Cont.)

24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the patient may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the consent is given to the patient.
29. The statement, "I agree to participate..."
30. A place for the patient or the patient's legally acceptable representative to sign and date.
31. A place for the person who conducted the informed consent discussion to sign and date.

Appendix E
Sample Abbott Laboratories Drug Accountability Form
Study M99-114

Subject Randomization Number:◆ _____ **Subject Initials:** _____ **Subject Birthdate:** _____

Investigator's Name: _____ **Location:** _____

	Module Carton Type	Module # ◆	NPRO #	Clinical Supplies Invoice No.	Date Received (M/D/Y)
Baseline Visit	Days 1–7				
Baseline Visit	Days 8–49				
Visit II	Days 8–49				
Visit III	Days 8–49				

Visit	DISPENSED TO SUBJECT					RETURNED FROM SUBJECT			VERIFIED BY CRA	
	Module # ◆	# Capsules	Date	By*	Checked By	Date	No. of Capsules Remaining	By*	By+	Date
Baseline Visit	Days 1–7 — — — — —	52								
	Days 8–49 — — — — —	144								
Visit I	Redispense balance of Days 8–49 cards remaining from Baseline Visit	— — —								
Visit II	— — — — —	144								
Visit III	— — — — —	144								

* Pharmacist/Coordinator/Nurse + CRO Monitor ◆ Assigned by IVRS

Appendix F
Pain Assessments

Pain Rating Scale (11 point Likert)

The subject's pain intensity will be assessed by completion of the following statement in the daily diaries and at the investigative site.

How severe was your neuropathy pain during the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Possible

Appendix G

Neuropathic Pain Scale

Instructions: There are several different aspects of pain which we are interested in measuring: pain **sharpness, heat/cold, dullness, intensity,** overall **unpleasantness,** and **surface vs. deep** pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."

Not sharp	0	1	2	3	4	5	6	7	8	9	10	The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain feels. Words used to describe very hot pain include "burning" and "on fire."

Not hot	0	1	2	3	4	5	6	7	8	9	10	The most **hot** sensation imaginable ("on fire")

4. Please use the scale below to tell us how **dull** your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most **dull** sensation imaginable

Appendix G (Cont.)

5. Please use the scale below to tell us how **cold** your pain feels. Words used to describe very cold pain include "like ice," and "freezing."

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most **itchy** sensation imaginable ("like poison oak")

8. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how **unpleasant** your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most **unpleasant** sensation imaginable ("intolerable")

9. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No deep pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense deep** pain sensation imaginable

10. **HOW INTENSE IS YOUR *SURFACE* PAIN?**

No **surface** pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense surface** pain sensation imaginable

Appendix H
Subject Global Impression of Change and Clinician Global Impression of Change

Subject Global Impression of Change

The subject's impression of pain relief will be assessed by completion of the following statement:

Compared to the Baseline Pain Assessment Phase, how much have you changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

Clinician Global Impression of Change

The clinicians impression of pain relief will be assessed by completion of the following statement:

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to Baseline, how much has the subject changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

Appendix I
Laboratory Determinations, Vital Signs and Electrocardiogram Variables for Statistical Analysis

Hematology	Below Limit	Above Limit
Hemoglobin (g/dL)		
Female	≤ 9.5	≥ 16.5
Male	≤ 11.5	≥ 18.5
Hematocrit (%)		
Female	≤ 32	≥ 50
Male	≤ 37	≥ 55
Red Blood Cells (x 10^{12}/L)		
Female	≤ 3.5	≥ 6.0
Male	≤ 3.8	≥ 7.0
White Blood Cells (x 10^9/L)	≤ 2.8	≥ 16.0
Platelet Count (x 10^9/L)	≤ 75	≥ 700
Eosinophils (%)		≥ 10
Basophils (%)		≥ 10
Lymphocytes (%)		≥ 75
Monocytes (%)		≥ 15
Neutrophils (%)	≤ 15	
Bands (%)		≥ 10
Mean Corpuscular Volume (fL)	≤ 0.8 x LLN	≥ 1.2 x ULN
Mean Corpuscular Hemoglobin Concentration (g/dL)	≤ 0.8 x LLN	≥ 1.2 x ULN
Atypical Lymphocytes (%)		≥ 5
Prothrombin Time (sec)		≥ 2 ULN
Partial Thromboplastin Time (sec)		≥ 2 ULN

LLN = Lower limit of normal ULN = Upper limit of normal

Appendix I (Cont.)

Chemistry	Below Limit	Above Limit
Albumin (g/dL)	≤ 2.5	
Alkaline Phosphatase (IU/L)		≥ 3 x ULN
Bicarbonate (mEq/L)	≤ 12	≥ 38
BUN (mg/dL)		≥ 30
Calcium (mg/dL)	≤ 8.2	≥ 12
Chloride (mEq/L)	≤ 90	≥ 118
Cholesterol (mg/dL)		≥ 600
Creatinine (mg/dL)		≥ 2.0
Direct Bilirubin (mg/dL)		≥ 2.0
Glucose (mg/dL)	≤ 45	≥ 175
LDH (IU/L)		≥ 3 x ULN
Inorganic Phosphorus (mg/dL)	≤ 1.7	≥ 5.5
Potassium (mEq/L)	≤ 3.0	≥ 6.0
SGOT/AST (IU/L)		≥ 3 x ULN
SGPT/ALT (IU/L)		≥ 3 x ULN
Sodium (mEq/L)	≤ 126	≥ 156
Total Bilirubin (mg/dL)		≥ 2.0
Total Protein (g/dL)	≤ 4.5	≥ 10
Triglycerides (mg/dL)		≥ 600
Uric acid (mg/dL) Female Male		 ≥ 8.5 ≥ 10.5

ULN = Upper limit of normal

Appendix I (Cont.)

Urinalysis	Below Limit	Above Limit
Specific Gravity	≤ 1.001	≥ 1.030
PH	≤ 4	≥ 9
Protein		≥ 3+* (≥ 10)
Ketones		≥ 3+*
RBC		
Female		≥ 10/hpf
Male		≥ 8/hpf
WBC		≥ 10/hpf (≥ 2+)
Casts		≥ 9
Glucose		≥ 3+*
Oral Body Temperature		
Temperature	Low: decreased ≥ 2°F from baseline	
	High: ≥ 101°F	
Body Weight		
Weight	Low: decreased ≥ 15% from baseline	
	High: increased ≥ 15% from baseline	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mmHg and decreased ≥ 30 from baseline	
	High: ≥ 180 mmHg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mmHg and decreased ≥ 20 from baseline	
	High: ≥ 105 mmHg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline	
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	

* ≥ 3+ on a scale with 4+ being the maximum value

Appendix I (Cont.)

Electrocardiogram	
PR Interval	High: ≥ 210 msec
QRS Duration	Low: ≤ 50 msec High: ≥ 150 msec
QT Interval	Low: ≤ 200 msec High: ≥ 500 msec
QTc Interval*	Low: ≤ 200 msec High: ≥ 500 msec
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline

* QTc calculated as QT divided by the square root of RR interval

EX. 20

Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
12/14/2000 12:20 PM

To JSCHANZENBACH@rsi-nc.com@internet
cc
bcc
Subject Study Termination

Hi John

We've decided to end enrollment as of 1/5/01. The attached letter (which explains our reasoning) will be fedexed out to all investigators today. You may get some phone calls tomorrow. Let me know if you have any questions. Thanks.....mc


stopenroll

Silber DEP. EX. NO. 39
FOR ID., AS OF 2-9-07 BC

EXHIBIT
McCarthy
29
9-29-06 cb

December 14, 2000

<name>
<address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr. <name>,

We have decided to end enrollment in the above referenced study on January 5, 2001.

As specified in the protocol, 80% power would have been achieved with the randomization of 320 subjects, assuming there were no premature terminations. Our current premature termination rate, however, will result in less than 80% power even if we were to reach our enrollment goal. After reviewing possible outcomes with our statisticians, we concluded that ending enrollment prior to reaching our goal of 320 subjects will not meaningfully change our ability to interpret the results of this study. In addition, the sooner we review the data from M99-114, the sooner we may be able to move forward into Phase III.

In order to allow you to enroll any subjects that may have already been scheduled, the last date for randomization into study M99-114 will be 1/5/01. We sincerely apologize if this causes you or your staff any inconvenience.

The Analgesia Venture thanks you for your hard work and dedication to ABT-594 and study M99-114. Your efforts have allowed us to move forward more quickly than anticipated. If you have any questions or concerns please don't hesitate to contact me.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

PLs' BY

James W Thomas

12/21/99 08:06 AM

To: Fred W Siebert/LAKE/PPRD/ABBOTT@ABBOTT, Kevin J Heuser/LAKE/PPRD/ABBOTT@ABBOTT
cc: (bcc: James W Thomas/LAKE/PPRD/ABBOTT)
Subject: 114 Sample Size

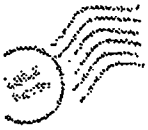
Below is my attempt at writing up the sample size section of the 114 protocol.

This study is designed to enroll approximately 320 patients (80 patients in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average Daily Pain Intensity score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two- tailed Type I error) level with at least 80% power. This calculation is based on results obtained from ABT-594 study M99-833 and published data using Gabapentin for patients with painful diabetic polyneuropathy (add reference here to Dec 1998 JAMA article) and assuming an 39% and 25% improvement from baseline for ABT-594 and placebo respectively.

Jim

Thomas DEP. EX. NO. 1
FOR ID., AS OF 4/13/07 Rpm

PLs' CJ



Bruce McCarthy /LAKE/PPRD/ABBOTT
07/07/2000 11:13 AM

To David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Andrea Landsberg/LAKE/PPD/ABBOTT@ABBOTT, Michael K Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT
cc Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject M99-114 Protocol Change Discussion

I've scheduled a meeting next week to discuss options to modify the 114 protocol. Enrollment has not met initial expectations. At the present rate of enrollment, data would not be available until June or July of 2001. We in the venture continue to work to address this situation by reasonable encouragement to sites and other modifications to the management of the study (including removal of poorly enrolling sites and replacement with back-up sites). Several protocol-related issues, however, may outweigh any encouragement or management strategies.

Of the 78 subjects enrolled to date, at least 31 have pretermed. Of those, at least 20 appear to have pretermed for AEs typical of our drug (nausea, vomiting and/or dizziness). Although three of these subjects dropped on day one (when they would have, at most, been exposed to 75 mcg), many of these subjects dropped in the 3-11 day time frame (the period of dose escalation resulting in 150 mcg BID at day 4, 225 mcg BID at day 6 and 300 mcg BID at day 8). Appropriately, the preterm rate has created investigator and coordinator reluctance to enroll (or, more particularly, individual sites' experience with preterms). One option to address this concern would be to remove the top dose (300 mcg BID). This doesn't address all of the issues, in that we continue to be blinded and don't know how many of these subjects that dropped out would have been randomized to 150 or 225 (assuming all events are drug related). We would, however, be responding appropriately to sites' concerns and may reduce their appropriate concerns about enrolling subjects because subjects would no longer risk randomization to the 300 mcg dose.

In addition, as with the prior study (833), there continues to be significant investigator and coordinator head-wind related to a study design that requires subjects to be off all analgesics. One option is to remove this requirement and allow subjects to enter the trial on some level of concomitant analgesia.

Please consider the ramifications of these and other possible protocol design changes in preparation for this meeting. Let's begin to discuss these possibilities for implementation in the next few weeks. The optimal enrollment time extends until 9/22/00 (in terms of date of randomization)-after that, subjects starting on drug would be in the study during the holiday season and enrollment is likely to decrease. Any changes should be incorporated into a protocol amendment to be signed off the week of 7/17 so that they can be distributed for IRB approval. That timeline might allow a majority (and I mean 50%) of sites to be able to implement the changes by mid August.

Thomas DEP. EX. NO. 7
FOR ID., AS OF 4/13/07

CONFIDENTIAL
ABBT0082516

PLs' CQ

James W Thomas /LAKE/PPRD/ABBOTT
08/29/2000 03:31 PM

To Catherine K Kacos/LAKE/PPRD/ABBOTT@ABBOTT
cc
bcc
Subject Re: M99-114 graph data

---------- Forwarded by James W Thomas/LAKE/PPRD/ABBOTT on 08/29/2000 03:31 PM ----------

David G Jaskela
08/29/2000 02:56 PM

To: James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: M99-114 graph data

ABT-594.ppt
JAMES W THOMAS

JAMES W THOMAS
08/29/2000 02:19 PM

To: David G Jaskela/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: M99-114 graph data

Attached and below is the data for the 2 graphs.....

OBS	SAMPLE SIZE	EFFECT	POWER	CON
1	20	0.45	0.28380	0.63263
2	25	0.45	0.34451	0.71836
3	30	0.45	0.40297	0.78719
4	35	0.45	0.45862	0.84132
5	40	0.45	0.51108	0.88313
6	45	0.45	0.56013	0.91489
7	50	0.45	0.60564	0.93867
8	55	0.45	0.64760	0.95624
9	60	0.45	0.68606	0.96906
10	65	0.45	0.72111	0.97831
11	70	0.45	0.75292	0.98492
12	75	0.45	0.78165	0.98959
13	80	0.45	0.80751	0.99287
14	20	0.50	0.33794	0.70980
15	25	0.50	0.41010	0.79473
16	30	0.50	0.47790	0.85768
17	35	0.50	0.54069	0.90310
18	40	0.50	0.59815	0.93511
19	45	0.50	0.65019	0.95719
20	50	0.50	0.69689	0.97215
21	55	0.50	0.73849	0.98212
22	60	0.50	0.77527	0.98865
23	65	0.50	0.80758	0.99288
24	70	0.50	0.83582	0.99557
25	75	0.50	0.86037	0.99728

26	80	0.50	0.88160	0.99834
27	20	0.55	0.39576	0.77939
28	25	0.55	0.47837	0.85807
29	30	0.55	0.55365	0.91108
30	35	0.55	0.62107	0.94559
31	40	0.55	0.68059	0.96741
32	45	0.55	0.73249	0.98086
33	50	0.55	0.77727	0.98895
34	55	0.55	0.81555	0.99372
35	60	0.55	0.84800	0.99649
36	65	0.55	0.87532	0.99806
37	70	0.55	0.89816	0.99894
38	75	0.55	0.91715	0.99943
39	80	0.55	0.93285	0.99970
40	20	0.60	0.45603	0.83904
41	25	0.60	0.54731	0.90723
42	30	0.60	0.62750	0.94832
43	35	0.60	0.69653	0.97205
44	40	0.60	0.75495	0.98529
45	45	0.60	0.80370	0.99244
46	50	0.60	0.84388	0.99619
47	55	0.60	0.87664	0.99812
48	60	0.60	0.90312	0.99909
49	65	0.60	0.92433	0.99957
50	70	0.60	0.94119	0.99980
51	75	0.60	0.95452	0.99991
52	80	0.60	0.96498	0.99996


smaller.lst

PLs' CS

August 31, 2000

<Investigator Name>
<Address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr.:

I am pleased to inform you that the enrollment period for study M99-114 has been extended. The last day for randomization will be March 2, 2001. If we reach our target enrollment before that date the study will be ended at the time when 320 subjects are randomized.

While it may now seem that we have a bit of breathing room, in actuality we don't. The holidays are fast approaching - a time when recruitment and enrollment slows down considerably. We will, in effect, be losing approximately 2 months of our enrollment extension to the holiday season. That will leave us with just 3 ½ months of remaining optimal recruitment time. To put this in perspective, in the last 3 ½ months of this study approximately 110 subjects were randomized. If we enroll the same number during the optimal recruitment period of the enrollment extension, we will have a total enrollment of 240 - 80 subjects short of our goal. These numbers indicate a need to remain focused on recruitment efforts before and after the holiday season.

We expect the holiday season to be challenging in terms of recruitment and enrollment, however, there may be an advantage for many subjects to enroll during this time. If a subject receives pain relief from the study medication, their holidays would be more enjoyable. In addition, subjects should be able to determine whether or not they will tolerate the drug within the first week of therapy. With careful planning of randomization dates, the issue of tolerability is unlikely to interfere with the subjects' holidays.

Please continue to use the upcoming weeks to concentrate your efforts on maximum recruitment and enrollment. Please continue to call us with your enrollment questions. The Analgesia Venture at Abbott Laboratories thanks you for your continuing efforts to make study M99-114 a success.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

PLs' DH

November 2000
ABT-594 Project Status Report

Monthly Highlights

- In-life phase of 2-year mouse carcinogenicity studies completed mid-November.
- Proposals and timelines from 3 patient recruitment firms were reviewed, with a conclusion reached that hiring a recruitment firm to increase enrollment for study M99-114 was not a viable option at this time.
- USAN approval for the generic / chemical name for ABT-594 was received. The United States Adopted Name for ABT-594 (A-166594.47) is ebanicline tosylate (ē-ba-ni-klēn to-se-lāt.)
- Preliminary commercial capsule design selected by AI and PPD Marketing, with input from across the project team. The primary parameters are: Size 3 hard gelatin capsules, 2 strengths / colors: 75 mcg - 1/2 light yellow, 1/2 white, 150 mcg – both halves light yellow, printed with strength and trade name (TBD.)

Key Progress Gauges - November Accomplishments	Target Date	Status
• Final decision on commercial capsule parameters to be provided by NPD to PARD	11/10	Complete – All information provided by 11/13.
• Achieve enrollment of at least 220 patients in M99-114 by 11/30	11/30	Complete – 246 patients enrolled as of 11/30
• Complete 7 "good will" site visits for M99-114	11/30	Complete

December Projections	Target Date	Status
• Portfolio analysis team review of forecast and expense projections	12/19	
• Achieve enrollment of at least 260 patients in M99-114 by 12/31	12/31	

November 2000
ABT-594 Project Status Report

Project Cost Summary – November

$000's Activity	Cumulative through 1999	YTD Actual	Projected Year-end	Current Funded Year-end	Variance	Cumulative to NDA
Clinical Program	22.9	7.0	7.6	7.9	.3	157.1
CMC (PARD & SPD)	13.0	3.0	3.2	2.6	-.6	27.6
Drug Safely	8.7	2.8	3.0	2.4	-.6	18.3
Other Support Costs	0.7	.5	.6	1.5	.9	12.2
Total	50.5	13.3	14.4	14.4	0.0	215.2

File NDA = 9/2003

Clinical Study Progress

Protocol # - Study Name	Start (1st *Patient Dosed*)	End (*Last CRF In House*)	Total R/OSS $000	Total Target Patients	Current Enrollment
M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	04/00	04/01	3,000	320	246 (as of 11/30)

November 2000
ABT-594 Project Status Report

Business Rationale

Date: November 2000
Franchise: Neuroscience
Venture: Analgesia

ABT #: ABT-594
Trade & Generic Name: TBD, ebanicline tosylate
Mechanism of Action: Neuronal Nicotinic Receptor (NNR) Agonist

Indications: Neuropathic Pain
Chronic Pain (publication only)

Product Profile

Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Not scheduled	12/1996	High	1Q04	High
Chronic nociceptive pain efficacy	10/1999	Medium	2Q01	High
Neuropathic pain claim	6/1999	Medium	2Q01	High
General pain claim Moderate to moderately severe pain	12/1996	N/A	N/A	High
No tolerance/dependence or withdrawal	9/1998	Medium	1Q03	High
Very few abnormal LFTs	9/1998	High	2Q01	High
Low nausea/vomiting at effective dose	6/1999	Medium	2Q01	High
Other safety OK	9/1998	Medium	2Q01/1Q03	High
No differential efficacy (nicotine users vs. non users)	9/1998	High	2Q01/1Q03	High
No differential side effect profile (nicotine users vs. non users)	9/1998	Medium	2Q01/1Q03	Medium
No reinitiation of cravings in ex-nicotine users	9/1998	N/A	N/A	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	Low	4Q01	Medium
Onset of action comparable to other therapies for neuropathic pain	6/1999	N/A	N/A	Medium
BID dosing	6/1999	High	2Q01	High
No major drug interactions	12/1996	High	1Q03	Medium
Titration of 2-5 days duration is required to minimize nausea and vomiting at effective dose.	9/1999	Medium	1Q00	High

* Probability Key:
High = 70-100%
Medium = 30-69%
Low = 0-29%

Market Forecast

	PPCC/DDC 12/1996*	Plan as of 6/1998*	Current Revised 10/2000**
Patent Status:	10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
NDA Filing:	12/1999 (acute) 6/2001 (chronic)	12/2001	9/2003
Ex-U.S. Filings:	Same as above – Eur N/A - Jpn	12/2001 - Eur 12/2003 - Jpn	9/2003
Projected U.S. Launch:	12/2001 (acute) 12/2002 (chronic)	6/2003	9/2004
Projected ex-U.S. Launches:	Same as above – Eur N/A - Jpn	12/2003 - Eur 9/20/2004 - Jpn	Q2 2005 ("average" launch for EU, LA, Canada) Q4 2005 (Average launch for Japan, PAA)
Peak TRx Share, U.S.:	6.6% (patients)	5% (Rx)	20% (Neuropathic pain) 10% (Persistent Chronic Pain)
Peak TRx Share, ex-U.S.:	5.4% (patients)	5% (patients)	same as US assumptions
Peak Sales, U.S.: ($MM)	$285	$618	$367
Peak Sales, ex-U.S.: ($MM)	$308	$310	$466
Pre-Tax NPV @ 15%, ex-U.S.: ($MM)	$338	$305	$359
After-Tax NPV @ 12.5%, U.S.: ($MM)	$412	$813	$296
Avg. daily dose	50 mg	200 mcg	150 mcg
Target Drug Cost/kg at Launch	$2,500	$2,500	$40,000 (base eq.)
SMM at Launch	94.8%	97.2%	98.6%
SMM at Year 5			

* Forecast based on general pain target indication
** Forecast based on neuropathic pain indication and published study in chronic pain

November 2000
ABT-594 Project Status Report

Project Overview

Metrics Dates

Description	Date
DDC Meeting	12/1996 (PPCC)
Start of first GLP animal tox study	2/1997
First dose in human (beg. Phase I)	7/1997
First dose in patient (beg. Phase II)	7/1998
First dose in Phase III	2/2002 (est.)
Last Patient/Last Visit	4/2003 (est.)
NDA Filing	9/2003 (est.)
NDA Approval	9/2004 (est.)
Europe (EMEA) Filing	9/2003 (est.)
Europe (EMEA) Approval	TBD
Japan Filing	4/2004 (est.)
Japan Approval	TBD

PARD

Activity	Plan 6/1999	Current Revised 10/00	Actual
Phase I Formulation (PIB)*	7/1997	7/1997	7/1997
Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)	10/1998	10/1998	10/1998
Phase IIb / Formulation (HGC) for Bio Study	3/1999	3/1999	3/1999
Phase III Clinical Supplies Manufactured	9/1999	9/2001	TBD
NDA Lots (3) Completed	6/2000	5/2002	TBD
Completion of 1 Year Stability for NDA	7/2001	7/2003	TBD
Formulation Peer Review	10/2001	TBD	TBD

* Performed by IDC

SPD

Drug Substance Source/Lot #	KG	Plan 6/1999	Actual Date	Plan 6/1999 Projected Cost/kg*
D-45L	0.3 KG	3/1997	3/1997	$ 200,000
CAPD	5.6 KG	3/1997	3/1997	$ 175,000
SICOR	14.9 KG	2/1998	2/1998	$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	5/1999	$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	On Test	$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	On Test	$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	On Test	$ 29,700

* Target cost of drug substance at launch is $20,000/ kg (Tosylate Salt)

Toxicology

Toxicology Activity	Plan Start 1999	Actual Start Date	Report Completed
Gene Toxicology	2/1997	9/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	--	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing

Clinical Study Progress

Protocol:	M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy
Objective:	The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.
ABT-594 Doses:	150 µg, 225 µg, and 300 µg twice daily (BID)
Comparator Doses:	Placebo
Target Enrollment:	320
Target Cost:	$3 MM
Actual Cost:	TBD
Status:	Ongoing – 246 patients randomized as of 11/30
Major Findings:	TBD

PLs' EK

CONFIDENTIAL

ABT-594

Descriptive Memorandum

February 2001

Abbott Laboratories

ABT-594 Opportunity Overview

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release).

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be $350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach $1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Currently, there is an unmet market need for novel neuropathic pain treatments such as ABT-594. Therefore, this compound is likely to be well received in this arena. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately $140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately $90MM in neuropathic pain. Neurontin has achieved only $53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded $12BB ($6.7BB U.S., $5.6BB Ex-U.S.)

Market Size / Prevalence

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

Competition, Current Marketed Products:

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
TOTAL	12.5	5.6%	N/A	N/A
Source: IMS, factored for neuropathic uses. N/A = not available				

1999 Key Neuropathic Pain Products, Estimated $ Sales				
Product/Class	1999 U.S. Sales ($MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales ($MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	$308	28.7%	$53	57.6%
carbamazepine	$17	13.1%	$87	2.5%
TCAs	$26	-3.3%	N/A	N/A
TOTAL	$351	21.7%	$140	10.1%
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets N/A = not available				

Competition, Products In Development

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

Analgesia Development Pipeline – Key Novel Agents				
Product	**Company**	**Mechanism**	**Phase**	**Comments**
pregabalin	Pfizer	Unknown; possibly through (2™ subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

Analgesia Development Pipeline – Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events. Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimoclomol) may decrease incidence of neuropathic pain; thereby decreasing . available market for ABT-594.

Product / Development Background

Scientific Rationale for ABT-594

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID, the maximum dose studied in this protocol. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients is anticipated to be included in the study.

Considerations

Target Profile:

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

Label Strategy:

BASE: Indicated for the treatment of diabetic neuropathic pain.

UPSIDE:
1) Treatment of pain associated with OA
2) Treatment of post-herpetic neuralgia
3) Treatment of neuropathic pain
4) Treatment of chronic pain
5) Treatment of cancer pain

Cost of Goods Sold:

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of $40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately $0.024 per day.

Pricing:

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately $95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMEA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately $1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be $0.90/day.

PLs' FZ

ABBOTT LABORATORIES

Clinical Study Report No. R&D/01/171

A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy

ABT-594/Protocol M99-114

31 July 2001

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Marilyn J. Collicott — 01 Aug 01 — Date
Clinical Project Manager, Analgesia Venture

David D. Morris, Ph.D. — 03 Aug 01 — Date
Assistant Director, Statistics

Bruce G. McCarthy, M.D. — 03 Aug 01 — Date
Medical Director, Analgesia Venture

Marleen H. Verlinden, Pharm.D., Ph.D. — 03 Aug 01 — Date
Vice President, Global Pharmaceutical Research and Development Neurology/Urology

FOR MARLEEN VERLINDEN

Abbott Laboratories

1.0 Title Page

ABBOTT LABORATORIES
Clinical Study Report R&D/01/171

A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy

ABT-594/Protocol M99-114

Development Phase:	II
Investigators:	Multicenter
Date First Subject Dosed:	24 April 2000
Date Last Subject Completed Dosing:	24 February 2001
Sponsor/Signatory:	Marleen H. Verlinden, Pharm. D., Ph.D. Vice President, Global Pharmaceutical Research and Development Neurology/Urology D42U, AP30 200 Abbott Park Road Abbott Park, Illinois 60064-6145 Phone: (847) 935-4096 Fax: (847) 938-1629
Report Date:	31 July 2001

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

2.0 Synopsis

Name of Company: Abbott Laboratories	**Individual Study Table Referring to Item of the Submission:** not applicable (N/A) Volume: N/A Page: N/A	*(For National Authority Use Only):* N/A
Name of Finished Product: ABT-594 Hard Gelatin Capsule (HGC)		
Name of the Active Ingredient: Abbott-165594		
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter	**Study Center:** Multicenter	
Publication (reference): not applicable		
Study Period (years): Date First Subject Dosed: 24 April 2000 Date Last Subject Completed Dosing: 24 February 2001	**Phase of Development:** II	

Objective:
The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

Methodology:
This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo for 49 days on an outpatient basis. Thirty-four sites were recruited in order to enroll approximately 320 subjects who met entry criteria for this study.

Prior to any study-specific procedures at the Screening Visit, an informed consent was signed by the subject and study eligibility determined.

Prior to study drug administration, subjects discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who met entry criteria were randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Primer Phase, subjects took BID doses of ABT-594 or placebo. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days. During the Treatment Phase, subjects returned to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). Subjects were to complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects underwent site-based assessments of their neuropathic pain at the Baseline Visit and at Treatment Visits I, II, III and IV. Subjects discontinued study drug administration after Treatment Visit IV and returned to the site for the Follow-Up Visit 7-10 days later.

Methodology (continued):
During the Primer and Treatment Phases, subjects were allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but were not allowed to take acetaminophen within 24 hours prior to a Treatment Visit).

Efficacy assessments included the Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change. Safety assessment included physical examination, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.

No. of Subjects Planned and Enrolled:
Planned: 320
Enrolled: 266
Completed: 138
Premature Discontinuations: 128

Treatment Group	Planned	Completed/Enrolled
Placebo	80	51/65
ABT-594 150 µg BID	80	40/65
ABT-594 225 µg BID	80	30/69
ABT-594 300 µg BID	80	17/67
TOTAL:	320	138/266

Diagnosis and Main Criteria for Inclusion:
Adult males and females at least 18 years of age, who weighed ≤265 pounds and who were judged to be in good health based on medical history, physical examination with vital signs, laboratory profile, and 12-lead ECG, who had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, good control (in the opinion of the investigator) of the their serum glucose for at least the last 3 months prior to the Screening Visit, and an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit, and who met all other selection criteria were eligible for study participation.

Test Product, Dose and Mode of Administration, Batch Number:

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Numbers
ABT-594 75 µg HGC, Formulation A-2	150, 225, and 300 BID	Oral	58-293-AR 61-312-AR

Duration of Treatment: 49 days

Reference Therapy, Dose and Mode of Administration, Batch Number:

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Number
Placebo for ABT-594 HGC	0	Oral	55-243-AR-01

Criteria for Evaluations:
Efficacy:
The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation was analyzed in a similar manner. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to Day 1 of the study.

Criteria for Evaluations (continued):

Efficacy:

Change from baseline to final and each evaluation was calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] physical component summary (PCS), and mental component summary (MCS).

The efficacy evaluations recorded at the Baseline Visit were used as the baseline score for efficacy evaluations assessed at the investigative site.

Pharmacokinetics:

Blood samples for ABT-594 plasma assay were to be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max}, and C_{trough} were determined.

Safety:

Safety was assessed by medical history, physical exam, vital signs, ECG, clinical laboratory testing, and adverse event monitoring.

Statistical Methods:

For all safety and efficacy analyses, the primary comparisons were between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables were analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary- and site-based pain ratings were analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) were compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 was explored, with and without placebo included. Other efficacy analyses were performed as appropriate.

Treatment-emergent adverse events were summarized by body system and COSTART term and compared using Fisher's exact test.

Mean change from baseline to minimum, maximum and final values were summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits were flagged in the data listings. Furthermore, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

Summary/Conclusions:

Efficacy Results:

ABT-594 at 150, 225, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores,

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Pharmacokinetic Results:

At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

Safety Results:

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Safety Results (continued):
Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

Conclusions:
ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

Date of Report: 31 July 2001

3.0 Table of Contents for the Individual Clinical Study Report

3.0 Table of Contents for the Individual Clinical Study Report (continued)

Page

List of In-Text Tables

List of In-Text Figures

4.0 List of Abbreviations and Definitions of Terms

List of Abbreviations

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or Abbott-165594
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CMH	Cochran-Mantel-Haenszel
DNA	Deoxyribonucleic acid
EDTA	Edetic acid
HGC	Hard gelatin capsule
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MCS	Mental component summary
nAChR	Nicotinic acetylcholine receptor
NCR	No carbon required
NPRO	New Product Research Order
OC	Observed cases
PCS	Physical component summary
SEC	Soft elastic capsule
SF-36™	Short Form-36 Health Status Survey
SSRIs	Serotonin-specific reuptake inhibitors
TENS	Trancutaneous electrical nerve stimulation

Terms

Hemoglobin A_{1c}	Glycosolated hemoglobin
NOMAD®	A data management system

5.0 Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator obtained a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories received documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol required IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals were required since the study was completed within 1 year. A complete list of documents required prior to initiation of the study is located in the study protocol (Appendix 16.1.1). Information regarding the IRB is presented in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version) and all applicable local regulations. The investigator ensured that the study was conducted in accordance with prevailing local laws and customs or complied with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in the study protocol (Appendix 16.1.1).

5.3 Subject Information and Consent

The investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of the Informed Consent are specified in the study protocol (Appendix 16.1.1). A sample copy of the informed consent is presented in Appendix 16.1.3.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study identified each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) were used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study were reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to ensure adequate source documentation, accuracy, and completeness of the CRFs.

The site collected information on the subject per International Conference on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who could be contacted in an emergency was also recorded. This information was treated with strict adherence to professional standards of confidentiality and was filed at the site.

Neither the subject, the subject's physician, nor the investigator were informed of the subject's pharmacogenetic results, if obtained. If performed, the pharmacogenetic results from individual subjects were kept confidential and were not given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples are being stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples are being kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Thirty-four investigators in the United States were recruited to perform the study and received study drug supplies. Twenty-nine of these investigators randomized at least 1 subject. The study was conducted from 24 April 2000 to 24 February 2001. Complete names, addresses, and affiliations of the principal investigators are included in Appendix 16.1.4. The distribution of all enrolled subjects for each investigator is presented by randomized treatment group in Table 6.1a.

Table 6.1a Distribution of Subjects by Investigator and Treatment Group

Investigator	Total Subjects Enrolled	Treatment Group			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Backonja	3	1	1	0	1
Baumel	15	4	4	4	3
Biton	7	1	2	2	2
Bromberg	13	3	3	4	3
DeBold	12	3	3	3	3
Drucker	6	1	1	2	2
Eisner	6	1	1	2	2
Forde	2	0	0	1	1
Fried	9	2	2	3	2
Gibson	18	5	5	4	4
Gleeson	7	2	2	2	1
Haag	6	1	1	2	2
Hewitt	8	2	2	1	3
Holmlund	5	1	1	1	2
Kafka	7	2	1	2	2
Kipnes	15	4	3	4	4
Kirby	10	3	2	3	2
Kluge	9	2	2	2	3
McGill	8	2	2	2	2
Rowbotham	4	1	1	1	1
Shaibani	17	4	5	4	4
Simmons	6	1	2	2	1
Singer	15	4	4	4	3
Sivakumar	9	2	3	2	2
Steel	8	2	2	2	2
Storey	13	3	4	3	3
Suri	3	1	1	0	1
Vinik	6	2	1	2	1
Weinstein	19	5	4	5	5
Total	**266**	**65**	**65**	**69**	**67**

Cross Reference: Table 14.1__1.1

6.2 Sponsor Information

The sponsor coordinated the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form were generated by Abbott Laboratories. The database for this study was created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories were responsible for the statistical analysis of the data. A copy of the signature page for the study summary with the signature of the Abbott Laboratories' responsible Medical Officer is included in Appendix 16.1.5.

6.3 Contract Research Organization

Abbott Laboratories delegated prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to the following Contract Research Organization (CRO) for the conduct of this clinical study:

Research Solutions Inc.
3200 Chapel Hill Nelson-Highway, Suite 100
P.O. Box 14561
Research Triangle Park, NC 27709
1-800-807-7462

The sponsor and CRO maintained contact in order to manage adequately the progress of the study. The CRO coordinated and performed all site visits and prepared trip reports, using the Abbott Laboratories format, for each visit performed. These reports detailed the activities conducted at all investigative sites and included all relevant observations. All trip reports were forwarded to Abbott Laboratories in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures.

6.4 Clinical Supply Management

Clinical supplies were prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories authorized the release of clinical supplies once the appropriate essential documents were received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

All subjects were centrally randomized by site and assigned to a treatment group (using the randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS was contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using the randomization supplied by Abbott Laboratories) was also assigned using the IVRS. Each site kept an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records, and records for return of clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) from the CRO checked drug accountability records regularly.

6.5 Central Laboratory

This study utilized 1 central laboratory. All protocol-specified clinical laboratory tests were performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214
(800) 462-8887

The ABT-594 plasma assays were performed under the supervision of Raymond Wieboldt, Ph.D. of the Drug Analysis Department of Abbott Laboratories, Abbott Park, IL.

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

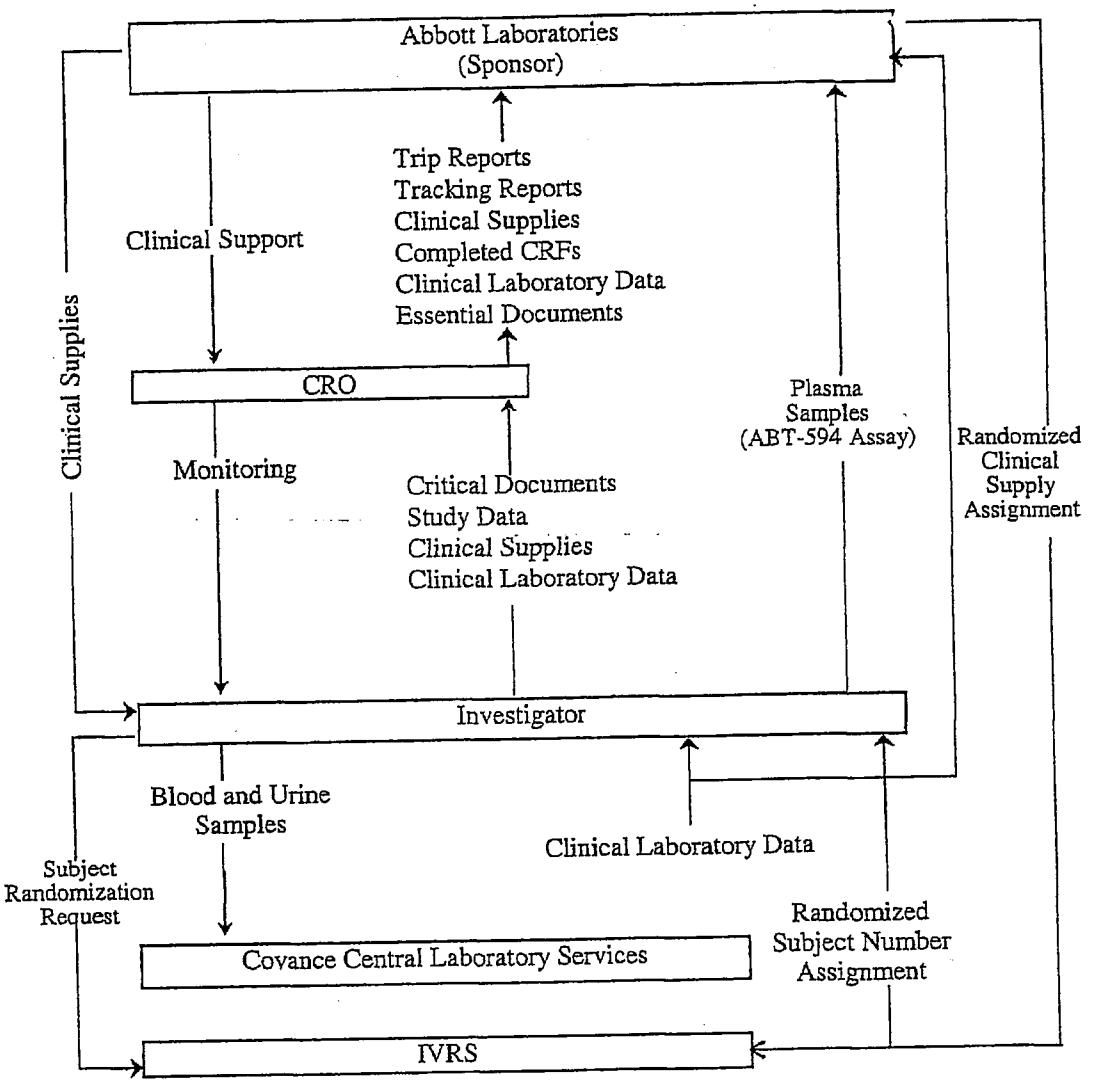


Figure 6.6a Administrative Structure

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.[1]

Currently there are 4 major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (±)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.[2] The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is

quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.[3] Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

Initial clinical trials in humans were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 μg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the

solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Preliminary data from Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120[4] included titrated doses up through 450 µg BID for 5 days. Results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout the Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

To date, Phase II trials have included efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon preliminary data from Study M97-772, a study of molar extraction pain, 100 µg ABT-594 (single-dose oral solution) appeared to be a minimally efficacious dose in acute pain.

A study of ABT-594 in osteoarthritis (M98-826)[5] evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks, and a study of ABT-594 in neuropathic pain (M98-833),[6] evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (≥5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature discontinuations).

Data from the Phase I and II studies completed to date suggest that ABT-594 should be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from the Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, was performed to test this hypothesis.

8.0 Study Objective

The objective of this study was to compare the safety and analgesic efficacy of 150 μg, 225 μg, and 300 μg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, had an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and had ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were to be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 μg, 225 μg, 300 μg BID or placebo for 49 days on an outpatient basis. Approximately 30 sites were to be recruited in order to enroll approximately 320 subjects who met entry criteria.

The study was divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 was the first day of study drug administration. Subjects were allowed a window of ± 3 days for each study visit. A schematic of the study design is presented in Figure 9.1a.

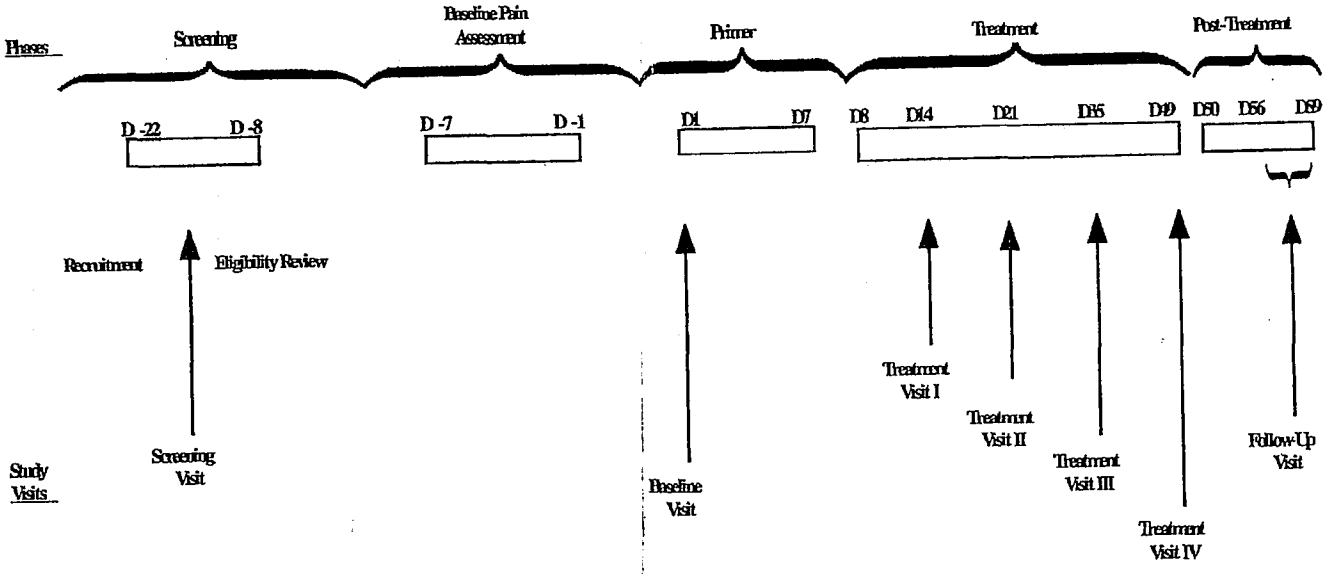


Figure 9.1a Study Schematic

Subjects reviewed and signed the informed consent prior to the conduct of any study specific procedures. Subjects were screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclic antidepressants, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs, or other analgesics for the treatment of their pain were to have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase. During the Baseline Pain Assessment Phase, at approximately 11 AM each morning, subjects were to complete the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity.

On the day after the Baseline Pain Assessment Phase, subjects returned to the site for their Baseline Visit (Day 1). At this visit, diaries were collected and reviewed. In addition, subjects were to complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who met all entry criteria, including an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, completed the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects underwent an interim medical history, physical examination, vital sign measurements, electrocardiogram (ECG), and clinical laboratory tests.

Subjects who met all entry criteria at the Baseline Visit were randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo. Subjects started study drug at the evening dose on Day 1. During the Primer Phase, subjects received a fixed dose escalation of ABT-594 or placebo (Section 9.4.1). The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days.

Throughout the course of the study, subjects were not permitted to take concomitant analgesics, except for limited doses of acetaminophen (3 grams daily maximum or 6 grams maximum during the Baseline Pain Assessment Phase, and 6 grams maximum

per week for each of the 7 weeks of the Primer and Treatment Phases; Section 9.4.7). Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of Treatment Visits I, II, III and IV.

Subjects were to complete the diary-based Pain Rating Scale each morning, 3 hours after taking their morning dose of study drug (approximately 11 AM). They returned to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV included collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III), and the following efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute; Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements, clinical laboratory tests (Treatment Visits I, III and IV), ECG (Treatment Visit IV only), and ABT-594 plasma assay collection (Treatment Visits I and IV only). A subset of subjects at selected sites underwent additional pharmacokinetic sampling at Treatment Visits I and IV.

On the day after Treatment Visit IV, subjects entered the Post-Treatment Phase. Subjects no longer took study drug or completed pain scales. Subjects could have restarted all discontinued medications under the guidance of their physician. Subjects returned for study procedures at the Follow-Up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-Up Visit included physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV, and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participated in clinical studies of ABT-594 and who consented, a blood sample was collected in order to obtain a sample of genetic material (deoxyribonucleic acid [DNA]). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a

genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

Copies of the protocol and amendment, and the CRF are included in Appendices 16.1.1 and 16.1.2, respectively.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provided a placebo-control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel-group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales were employed.

9.3 Selection of Study Population

Approximately 320 subjects were to be randomized and receive study medication in this study. A subject was randomized in this study provided that he/she met all of the inclusion criteria outlined in Section 9.3.1 and did not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

A subject was to meet all of the following criteria within 22 days before the initial dose of study drug:

1. Prior to any study specific procedure, voluntary written informed consent was obtained from the subject after the purpose and nature of the study were explained.
2. The subject was age 18 or older and in relatively good health with a recent stable medical history.
3. The subject's weight was ≤ 265 pounds.

4. A female subject was to be non-lactating and:
   - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation), or
   - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and continued the contraceptive method through the course of the study).

   All female subjects had a negative β subunit human chorionic gonadotropin (β-hCG) at the Baseline Visit. Female subjects of childbearing potential had a negative β-hCG at all Treatment Visits.
5. The subject had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, and good control (in the opinion of the investigator) of the subject's serum glucose for at least the last 3 months prior to the Screening Visit.
6. The subject had distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.
7. The location and quality of the pain under study were consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
8. The subject had distal symmetric diabetic polyneuropathy symptoms (including pain) which were stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
9. The subject had an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

A subject was to be excluded from participation in the study for any of the following reasons:

1. The subject had a positive test result for drugs of abuse or viral hepatitis at the Screening Visit, or had a known history of a positive test result for HIV.
2. The subject had recent (<5 years) history of drug or alcohol abuse or dependence.
3. The subject had an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.

4. The subject had an active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that had been treated or other malignancies that had been surgically removed and had no evidence of recurrence for a minimum of 5 years prior to study start).

5. The subject had taken an investigational drug within 1 month prior to administration of study treatment or was scheduled to receive an investigational drug other than ABT-594 during the course of this study.

6. The subject had a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.

7. The subject had orthostatic hypotension (defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing) at the Screening Visit, or a history of syncope or pre-syncopal symptoms.

8. The subject had previously participated in a study involving ABT-594, including the present study.

9. The subject had clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$ 1.5 times the upper limit of the reference range, a serum creatinine >1.5 mg/dL or a hemoglobin A_{1c} >11% (subjects may have had elevated serum and urine glucose).

10. The subject had clinically significant electrocardiographic abnormalities.

11. The subject had ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.

12. The subject had a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject could not differentiate from the neuropathy pain.

13. The subject had sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.

14. The subject was unlikely to comply with the study protocol or was unsuitable for any other reason, in the opinion of the investigator.

9.3.3 Removal of Subjects from Therapy or Assessment

A subject could have voluntarily discontinued participation in the study at any time. The investigator may also have decided, for medical reasons or protocol noncompliance, to discontinue prematurely a subject's participation. The investigator was to notify the CRA within 24 hours and document the reason for premature discontinuation on the appropriate CRF.

Subjects whose participation was discontinued prematurely after signing study consent but before study drug administration did not require follow-up observations. Subjects whose participation was discontinued prematurely after study drug administration were to undergo the procedures normally performed at Treatment Visit IV within 7 to 10 days following discontinuation from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represented a significant risk to subjects, the study was to be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID
ABT-594 225 µg BID
ABT-594 300 µg BID
Placebo for ABT-594 BID

ABT-594 and matching placebo were supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects received a fixed dose escalation of study drug. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4a.

Table 9.4a ABT-594 Dose Escalation

Treatment Group	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594 BID	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594 BID	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594 BID	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

During the Primer Phase, subjects randomized to placebo received a fixed dose escalation of placebo BID, in a double-blind fashion.

Subjects started study drug at the PM dose on Day 1 (Section 9.4.5). The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4b.

Table 9.4b Number and Type of Capsules by Treatment Group

Treatment Group	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg BID	2	2
ABT-594 225 µg BID	3	1
ABT-594 300 µg BID	4	0
Placebo BID	0	4

9.4.2 Identity of Investigational Product(s)

Information regarding the formulations used in this study is presented in Table 9.4c.

Table 9.4c Identity of Investigational Products

Test Preparation	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR 61-312-AR	52-015-KD-00	Abbott[a]
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	not applicable	Abbott[a]

[a] PARD Solids Pilot Plant, North Chicago, Illinois.

The ABT-594 75 µg HGC and placebo HGC were identical in appearance.

A listing of subjects receiving test preparations/investigational products from specific batches is presented in Appendix 16.1.6.

9.4.2.1 Packaging and Labeling

Study drug supplies were blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards were provided to each subject.

Daily study medication cards were labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space was provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies were stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies were stored at controlled room temperature (68-77° F, see USP).

9.4.2.3 Drug Accountability

The investigator or designee verified that study drug supplies were received intact and in the correct amounts. This was documented by signing and dating the Clinical Supplies Invoice or similar document. Study drug was dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who met the enrollment criteria. The investigator or designee recorded the subject number, subject initials, and date the study drug was dispensed to the subject on the Abbott Laboratories Drug Accountability Form. The amount of study drug remaining was recorded at Treatment Visits I, II, III and IV for each subject on the M99-114 Final Drug Supply Reconciliation Summary by Investigator Form. An accurate running inventory of study drug was kept and included the NPRO number, Clinical Supplies Invoice number(s), the number of modules dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug was performed and verified by the CRA throughout the study and at the site close-out visit. All supplies (unused and empty blister cards) were inventoried, accounted for, and returned to Abbott Laboratories. A copy of the Return of Investigational Drug Supplies for Disposal Form, in accordance with the instructions of the CRA, was also included in the shipment. The investigator agreed not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule was computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects were centrally randomized by investigative site using an IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site.

Approximately 320 subjects were to be randomized in an equal ratio to receive either ABT-594 150 µg, 225 µg, 300 µg BID or placebo. Subjects were assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

The randomization schedule is presented in Appendix 16.1.7.

9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects started study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects then took BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs were to be taken with at least 1 cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject remained blinded to the subject's treatment throughout the course of the study. The study blind may have been broken if, in the opinion of the investigator, it was in the subject's best interest to know the study drug assignment. The sponsor was to be notified before breaking the blind, unless identification of the study drug was required for emergency therapeutic measures. Blind breaking information was to be provided using IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site. The sponsor was to be notified within 48 hours of the blind being broken. The date and reason for blind breakage were to be recorded on the appropriate CRF.

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks was taken.

Concomitant analgesics (prescription or over-the-counter [OTC], except aspirin and acetaminophen as described below), including (but not limited to) serotonin-specific reuptake inhibitors, mixed serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, NSAIDs, COX-2 inhibitors, muscle relaxants, transcutaneous electrical nerve stimulation (TENS) and topical analgesics were not allowed. In addition, St. John's Wort was not allowed.

Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, was permitted. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication was necessary during the course of this study, the medication name, dosage information, frequency and dates of administration was reported on the CRF. Concomitant analgesic medication use (frequency only) was recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and at Treatment Visits I, II, III and IV. The concomitant medication use record included the number of separate occasions each subject had used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects were instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance was documented by the investigator or designee on the M99-114 Final Drug Supply Reconciliation Summary by

Investigator Form and on the appropriate CRF. Overdose information was collected on the appropriate CRF.

9.5 Efficacy, Pharmacokinetic and Safety Variables

9.5.1 Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Study procedures were performed as summarized in Table 9.5a, Study Procedures Flow Chart.

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D -22 and D -8	Baseline Pain Assessment Phase D -7 to D -1	Primer Phase D1-D7		Treatment Phase D8-D49					Post-Treatment Phase D50-D59
						Treatment Visit				
	Screening Visit	D -7 to D -1	Baseline Visit D1	D2-D7	D8-D49	D14 I	D21 II	D35 III	D49 IV[a]	Follow-Up Visit D56 to D59
Informed Consent	X									
Medical History	X		X[b]						X	X
Physical Exam	X[c]		X			X		X	X	X
Vital Signs	X[d]		X[e]						X	X[f]
ECG			X			X		X	X	X[f]
Clinical Laboratory Tests[g]	X									
Viral Hepatitis Screen	X									
Urine Drug and Alcohol Screen	X		X			X[h]	X[h]	X[h]	X[h]	
Pregnancy Test			X							
Genetic Polymorphism Sample (If Applicable)						X			X	
ABT-594 Plasma Assay						X			X	
ABT-594 Pharmacokinetic Profile[i]	X		X			X	X	X		
Diary Issued			X			X	X	X	X	
Diary Collected		X		X	X					
Diary-Based Pain Rating Scale[j]			X			X	X	X	X	
Site-Based Pain Rating Scale			X			X	X	X	X	
Neuropathic Pain Scale									X	
Subject/Clinician Global Impression of Change			X						X	
SF-36™			X							
Randomize Subject			X			X[k]	X	X		
Dispense Study Drug			X			X	X	X	X	
Analgesic Use Monitoring			X			X	X	X	X	X
Adverse Event Monitoring			X			X	X	X	X	X
Concomitant Medication Monitoring			X			X	X	X	X	
Study Drug Accountability										

a Or upon premature discontinuation.
b Interim history.
c Included height.
d Included orthostatic measurements at Screening Visit only.
e Included oral temperature at Baseline Visit only.
f Performed only if there were clinically significant abnormalities at the previous evaluation.
g Chemistry, hematology and urinalysis.
h Required of all females of child-bearing potential.
i Study drug was to be taken in front of study staff. Blood samples from selected subjects were taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.
j To be completed at approximately 11 AM each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.
k Redispensed study medication for days 15-20 after checking drug accountability.

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer instructed the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) was the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments included the diary- and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements were to be performed 3 to 4 hours post dose, when possible.

Pain Rating Scale (11-Point Likert Scale)

Subjects were to assess pain intensity daily by completing the Pain Rating Scale in their diaries. These assessments were to be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects were to record the time they completed the assessments in their diaries.

Subjects also were to assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments were to be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation). The time of assessment was recorded on the appropriate CRF.

Neuropathic Pain Scale

The Neuropathic Pain Scale was completed by subjects at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation).

Subject Global Impression of Change

The Subject Global Impression of Change of analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

Clinician Global Impression of Change

The Clinician Global Impression of Change of a subject's analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) was completed by each subject at the Baseline Visit and at Treatment Visit IV (or upon premature discontinuation).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative explained the nature of the study to the subject and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

Medical History

A complete medical history was obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening was recorded. The medical history was updated at the Baseline Visit.

Physical Examination

A physical examination, including weight, was performed at the Screening Visit, Baseline Visit, Treatment Visit IV, and Follow-Up Visit. Height was measured at the Baseline Visit only. The physical examination performed at the Baseline Visit served as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate were measured at the Screening Visit, Baseline Visit, Treatment Visits I, III, and IV, and Follow-Up Visit. Orthostatic blood pressure and pulse rate were measured at the Screening Visit only. Oral temperature was taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit served as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) were obtained after the subject had been sitting for at least 3 minutes. Orthostatic measurements were obtained after 3 minutes in the supine position and then after 1 minute in the standing position. Ideally, the subject's blood pressure was to be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurements were to precede, not follow, scheduled blood draws. Subjects were kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

Electrocardiogram (ECG)

A resting 12-lead ECG was obtained at the Baseline Visit and at Treatment Visit IV. An ECG was performed at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The ECG performed at the Baseline Visit served as the baseline ECG.

A qualified physician interpreted the ECG. One copy of each 12-lead ECG and physician's report was retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples were obtained for the clinical laboratory tests presented in Table 9.5b at the Screening Visit, Baseline Visit, and Treatment Visits I, III, and IV. Laboratory tests were obtained at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The laboratory test results obtained at the Baseline Visit served as the baseline results (except for hemoglobin A_{1c}, for which the result obtained at the Screening Visit was used as the baseline result). Blood draws were to be performed after pain assessments or vital sign determinations during a visit.

Table 9.5b Clinical Laboratory Tests

Hematology	Blood Chemistry	Urinalysis
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total Bilirubin	pH
White Blood Cell (WBC) count	Aspartate Aminotransferase/ Serum Glutamic-Oxaloacetic Transaminase (AST/SGOT)	Bilirubin
Neutrophils	Alanine Aminotransferase/ Serum Glutamic-Pyruvic Transaminase (ALT/SGPT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline Phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Lymphocytes	Chloride	
Hemoglobin A_{1c} (Screening Visit and Treatment Visit IV only)	Calcium	
Mean Corpuscular Hemoglobin (MCH)	Inorganic Phosphorus	
Mean Corpuscular Hemoglobin Concentration (MCHC)	Uric Acid	
Mean Corpuscular Volume (MCV)	Bicarbonate	
Platelet count (estimate was not acceptable)	Cholesterol	
Prothrombin Time (PT)	Total Protein	
Partial Thromboplastin Time (PTT)	Glucose	
	Triglycerides	
	Albumin	

A central laboratory was utilized to process and provide results for the clinical laboratory tests.

The investigator reviewed all laboratory test results and assessed the clinical significance for each abnormal result. All laboratory test results that were considered clinically significant by the investigator were followed to satisfactory resolution. A copy of each laboratory report was included with the CRF.

Viral Hepatitis Screen

At the Screening Visit, subjects underwent serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody). The hepatitis test panel was performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens, collected at the Screening Visit, were tested for drugs of abuse and alcohol by the central laboratory.

Pregnancy Test

A urine pregnancy test was performed by designated study personnel at the Baseline Visit for all female subjects and at Treatment Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female was not eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected event(s) such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject. Subjects were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken.

All adverse events, whether in response to a query, observed by site personnel, or spontaneously reported by the subject were reported on the appropriate CRF. All adverse events and post-treatment laboratory abnormalities considered clinically significant by the investigator were followed to a satisfactory resolution.

The investigator assessed and recorded any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known),

severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must have been of a similar nature and severity.

The investigator used the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator used the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly related, probably not related, or not related to study drug was given, an alternate etiology was provided for the adverse event.

Adverse events (including those that met regulatory criteria for a serious adverse event) were monitored continuously from the time of study drug administration to the

Follow-Up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature discontinuation) were collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects were instructed to report to the investigator any other adverse events that occurred after the Follow-Up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures, that occurred after signing the informed consent and prior to the first dose of study drug were also collected.

Any abnormal laboratory value or change in vital signs was not documented as an adverse event unless it was a reason for premature discontinuation from the study, required treatment, or met regulatory criteria for a serious adverse event.

Ongoing medical conditions were considered adverse events if there was an increase in severity or frequency of occurrence. Since measurements of pain intensity were efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study was not considered an adverse event for the purposes of this study.

Serious Adverse Events

If an adverse event met any of the following criteria, whether related to study drug or not, the investigator and other professional personnel in attendance was to be notified as soon as possible for the appropriate action. The investigators were to notify Abbott Laboratories by telephone within 24 hours of being made aware of any serious adverse event. In addition, a written confirmation of the occurrence, including any supplementary data, was to be sent within 3 days of the telephone report.

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions were to be reported to Abbott Laboratories as serious adverse events.

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study were validated and considered standard for this population. All clinical and laboratory procedures in this study were standard and generally accepted.

9.5.3 Efficacy Variables

9.5.3.1 Primary Variable

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variables

Change from baseline to final and each scheduled evaluation was calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each evaluation only
- Site-based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health][7] physical component summary (PCS), and mental component summary (MCS).[8]

The pain evaluations recorded at the Baseline Visit were used as the baseline score for pain evaluations assessed at the investigative site.

9.5.4 Drug Concentration Measurements

Blood samples for ABT-594 plasma assay were to be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) was to be collected into a sodium heparin evacuated collection tube at each visit. Blood draws were to be performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinued, a blood sample was to be taken for ABT-594 assay at the premature discontinuation visit, and the exact time at which the prior dose was taken was to be recorded.

For those subjects participating in the additional pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), blood samples were collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject was instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication was taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit accommodated a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples were collected as follows: just prior to dosing (0 hour) and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects received their 8 PM dose as scheduled. Subjects were confined at the site until the 8-hour blood sample was collected.

All blood samples were immediately stored at 4°C or below. The samples were to be separated by centrifugation within 1 hour after collection. The supernatant was to be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information was also recorded on the appropriate CRF. All labeled plastic vials were placed in a rack to prevent breakage. Plasma samples for determination of ABT-594 were frozen at -5°C or colder within

1 hour from centrifugation. All specimens were kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the days of plasma assay blood draws, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draws were recorded on the CRF.

Details of the ABT-594 assay methodology will be presented in the Clinical Pharmacokinetic Report.

9.5.5 Pharmacokinetic Variables

For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max}, and C_{trough} were to be calculated using noncompartmental methods.

9.5.6 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples were collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to Covance Central Laboratory Services.

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis are not reported with this study summary. The samples may also be used for development of a diagnostic test for drug response.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting was held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting entailed a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site were trained on the study procedures by a CRA at a study initiation visit and given a CRF completion workbook for reference. The CRAs monitored each site approximately every 4 weeks. At each visit, 100% source-document review was made against the entries on the CRFs and a quality-assurance check was performed to ensure that the investigator was complying with the protocol and regulations. The investigator agreed to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs were retrieved by the CRA, a review of the data was conducted by a physician and a clinical review team at Abbott Laboratories.

The SF-36™ Health Status Survey (Acute) was recorded directly on the CRF and was considered source data.

All CRFs were to be legible and completed in black ball point ink. All corrections were initialed and dated by the investigator or designated assistant. The investigator reviewed the CRFs for completeness and accuracy and signed and dated the set of CRFs where indicated.

Each CRF was printed on 3-part no carbon required (NCR) paper. The forms consisted of a white, yellow and pink copy. The white and yellow copies of the completed, verified CRF were collected by the CRA and the pink copy was retained at the investigative site.

Data captured on the CRF were entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF were reviewed and corrected on-line. After completion of the entry process, computer logic checks were run to check for such items as inconsistent study dates and outlying laboratory values, and

any necessary corrections were made to the database and documented via addenda or audit trail.

The laboratory results were electronically transferred from the central laboratory to the study database. A final review of all laboratory results was conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests were 2-tailed and considered statistically significant if the P-value (Type 1 error rate) was less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest were between each ABT-594 treatment group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons were to be made as considered necessary. No statistical adjustments were made for multiple comparisons.

The baseline for all variables (except for the diary-based Pain Rating Scale) was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to the subject receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses were to be performed for 2 sets of data: intent-to-treat (ITT) subjects and evaluable subjects. Subjects who received at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale) were included in the ITT

analyses. The evaluable dataset included subjects who received at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses were performed with all randomized subjects who received at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements was assessed. The analyses were performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation was calculated for all efficacy variables (except both Global Impression of Change scores).

Primary Efficacy Analysis

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable were evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment

group by study center interaction. If the interaction term was not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences was to be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers had fewer than 1 subject per treatment group in the ITT dataset, data from such centers were to be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert Scale) score were assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change were analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS could have also been analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation were assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert Scale). For the diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each scheduled evaluation was analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change was evaluated using CMH methodology on actual scores.

If indicated, exploratory analyses were to be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

Dose response for ABT-594 was explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites was not significant, then the nonparametric Jonckheere-Terpstra test was to be used instead of Page's test to assess dose response of ABT-594.

Other analyses were to be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, were performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely discontinue for lack of efficacy. The "observed cases" (OC) analysis did not estimate the missing evaluation, and a subject who did not have pain evaluation on a scheduled visit was excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item was calculated, when less than ½ (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

9.7.1.4 Pharmacokinetic Analyses

The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the trough plasma concentration (C_{trough}) were to be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) were to be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{max}, dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{max} from the subset of subjects participating in the additional pharmacokinetic sampling were to be subjected to a mixed effects model analysis. The model was to include dose, visit (Treatment Visit I and Treatment Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine-use status, and other variables that may have accounted for variability in pharmacokinetics were to be included as covariates. The study center factor was to be included in the initial model, including a center main effect and, interaction of center with other factors. The center factor, or at least the interaction terms involving center, were to be dropped from the model if they explained little of the variability in the data. If the number of subjects who had only Treatment Visit I data and not Treatment Visit IV data exceeded 20% of the subjects with additional pharmacokinetic sampling, then the analyses were also to be performed for each visit separately. The hypothesis of invariance with dose was to be tested by comparing the 300 µg BID dose versus the 150 µg BID dose. If the hypothesis of dose proportionality was rejected in a comparison, then the 225 µg BID dose was to be compared to each of the 150 and 300 µg BID doses. If the visit by dose interaction was statistically significant, then a comparison was to be made for each visit.

An exploratory analysis was also to be performed on the data set obtained from all subjects (including those who did not participate in the additional pharmacokinetic sampling). This analysis was to take into account the appropriate time of sampling

relative to dosing. The questions of dose proportionality and change from Treatment Visit I to Treatment Visit IV were to be considered in this analysis.

If there was some evidence from the data of this study that ABT-594 was efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable was to be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration was to utilize the data of all subjects. An analysis using only the data of subjects undergoing additional pharmacokinetic sampling was also to be performed. The model was to include effects for efficacy variable baseline value and for visit. The center factor was to be incorporated appropriately. The dependency of the measurements from the same subject was to be accounted for. Other analyses were to be performed as necessary.

9.7.1.5 Safety Analyses

All subjects who received at least 1 dose of study drug were evaluated for safety.

Adverse events were coded using the COSTART V9 dictionary. Treatment-emergent adverse events (i.e., those which began or worsened in severity after randomized study drug was taken) were tabulated by body system and COSTART term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, was presented for each treatment group. Analyses by subgroup were performed as appropriate.

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the change from baseline to the minimum, maximum, and final values during the study for each laboratory variable.

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) was summarized.

Laboratory data values were categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values were flagged in the data listings. In addition, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG were analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfied the criteria for below and above limits were identified.

Concurrent medication use was summarized by treatment group.

Additional safety analyses were to be performed as indicated.

9.7.2 Determination of Sample Size

The study was designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size should have allowed for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation was based on results obtained from Study M98-833[6] of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy[10] and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

Significant changes in the developmental strategy of ABT-594 resulted in the study being prematurely discontinued by the sponsor. Therefore, although the protocol specified that approximately 320 subjects (80 per treatment group) were to be enrolled, enrollment was stopped at 266 subjects.

The final clinical protocol incorporated Amendment Number 1. All subjects were enrolled under the final protocol (Table 14.1__2). Full details of the clinical protocol and its amendment are presented in Appendix 16.1.1. Important changes included in the amendment are summarized below:

Amendment 1 (29 February 2000)

- Modified the inclusion criteria such that subjects were required to have good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit.
- Added that subjects with a hemoglobin A_{1c} >11% were to be excluded.
- Added hemoglobin A_{1c} at the Screening Visit and Treatment Visit IV and deleted the hemoglobin A_{1c} at the Baseline Visit.
- Added mixed serotonin and norepinephrine reuptake inhibitors and St. John's Wort to the list of excluded medications.
- Added that the Screening hemoglobin A_{1c} result served as the baseline result.

9.8.2 Statistical Changes

Although not specified in the protocol, efficacy analyses were also performed on a dataset that included subjects who did not prematurely discontinue from the study (study completers).

The change from baseline of the average diary-based Pain Rating score from each subject's diary to the corresponding average of each of the consecutive 7-day intervals after the first dose of study drug was summarized using both LOCF and OC techniques.

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to final, was analyzed for the following variables: diary- and site-based average Pain Rating Scale scores and Neuropathic Pain Scale Total Scores. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

10.0 Study Subjects

10.1 Disposition of Subjects

The location of premature discontinuation data is presented below.

Assessment	Statistical Analyses Table	Individual Subject Listing Appendix
Number and Percentage of Subjects Prematurely Discontinued	14.1__3.1	16.2__1.1
Listing of Subject Numbers by Reason for Premature Discontinuation	14.1__3.2	16.2__1.1
Subjects Who Prematurely Discontinued and Any Adverse Events for Which Study Drug was Prematurely Discontinued	14.1__3.3	16.2__1.1 16.2__7.1.1
Number of Subjects Who Prematurely Discontinued by Days of Exposure to Study Drug	14.1__3.4	16.2__1.1 16.2__5.1.1 16.2__5.1.2
Number and Percentage of Subjects that Prematurely Discontinued for Each Investigator	14.1__3.5	16.2__1.1
Previous and Concurrent Medications (Subjects Who Prematurely Discontinued)	none	16.2__1.1 16.2__1.2

Two hundred sixty-six (266) subjects were enrolled by 29 investigators. Of the 266 subjects, 65 were randomized to receive placebo, 65 were randomized to receive ABT-594 150 μg BID, 69 were randomized to receive ABT-594 225 μg BID, and 67 were randomized to receive ABT-594 300 μg BID. All 266 subjects who received study drug are included in the analyses of all treated subjects. Additionally, 3 subjects were randomized although they failed to meet admission criteria. These subjects did not receive study drug and are not included in the database.

The proportion of subjects prematurely discontinuing from the study was statistically significantly different among the treatment groups, with 14 (22%) subjects in the placebo treatment group, 25 (38%) subjects in the ABT-594 150 μg BID treatment group, 39 (57%) subjects in the ABT-594 225 μg BID treatment group, and 50 (75%) subjects in the ABT-594 300 μg BID treatment group. A statistically significant difference was also observed among the treatment groups for the proportion of subjects prematurely discontinuing from the study due to 1 or more adverse event, which was the most frequently reported reason for premature discontinuation (9% placebo, 28% ABT-594 150 μg BID, 46% ABT-594 225 μg BID, and 66% ABT-594 300 μg BID). Subject disposition is presented in Table 10.1a.

Table 10.1a Disposition of Subjects

	Treatment Group n (%)			
		ABT-594		
	Placebo	150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
All Treated Subjects	65	65	69	67
Completed Study	51 (78%)	40 (62%)	30 (43%)	17 (25%)
Prematurely Discontinued[a]	14 (22%)	25 (38%)	39 (57%)	50 (75%)
Adverse Event	6 (9%)	18 (28%)	32 (46%)	44 (66%)
Lack of Efficacy	6 (9%)	6 (9%)	2 (3%)	5 (7%)
Withdrew Consent	2 (3%)	3 (5%)	6 (9%)	5 (7%)
Subject Noncompliant	1 (2%)	3 (5%)	4 (6%)	2 (3%)
Lost to Follow-up	0	0	1 (1%)	2 (3%)
Other[b]	1 (2%)	1 (2%)	3 (4%)	2 (3%)

[a] Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

[b] Description of reason designated as "other": subject stopped taking study drug (2 subjects), initiation of exclusionary medication, medical records noting subject is an alcoholic, refusal to return for follow-up, out of town for 6 weeks, and randomization error (1 subject each).

Cross Reference: Tables 14.1__3.1 and 14.1__3.3 and Appendix 16.2__1.1

A graphic disposition of all subjects is presented in Figure 10.1a.

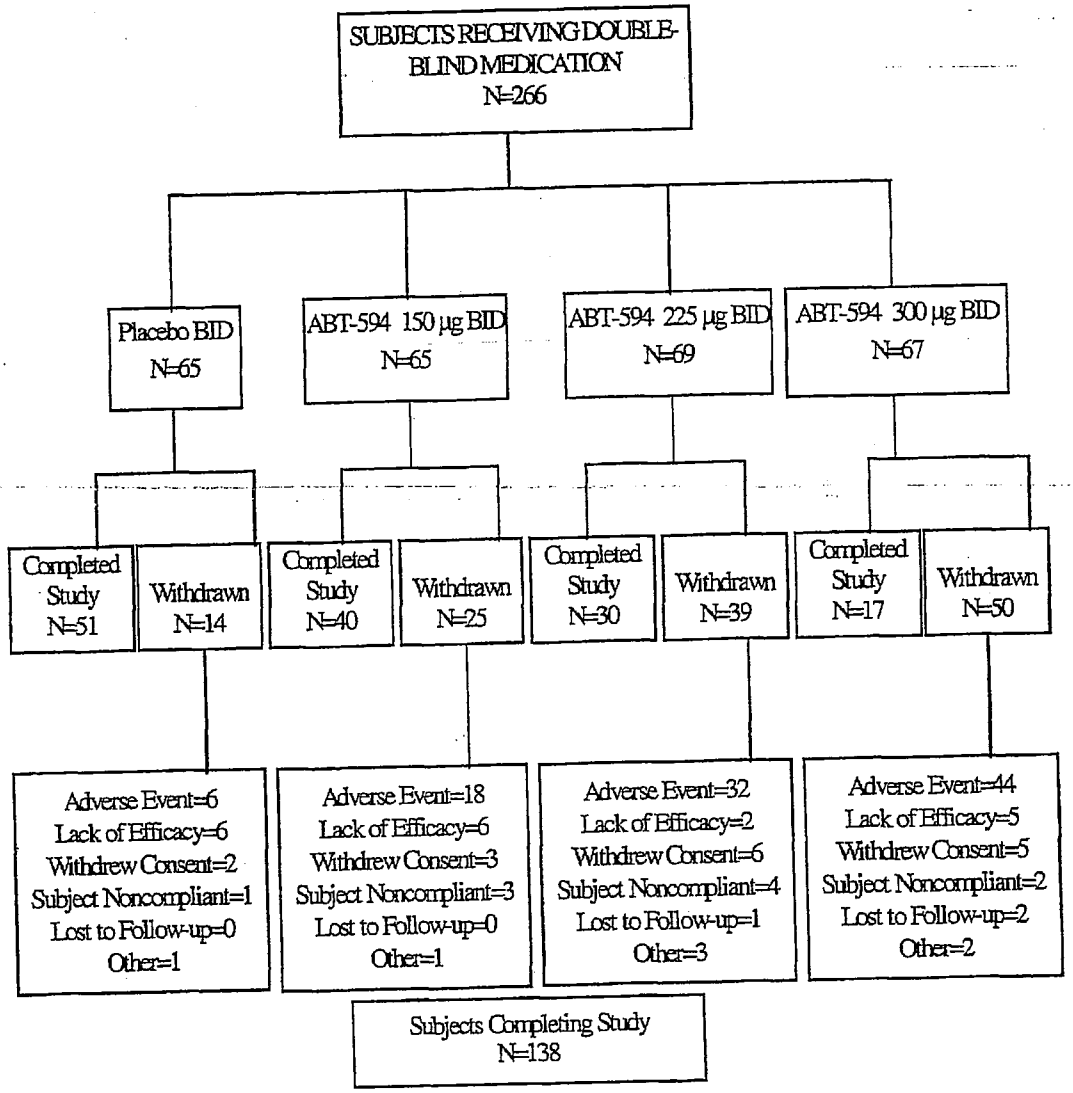


Figure 10.1a Disposition of Subjects

Note: Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

10.2 Protocol Deviations

The location of protocol deviation data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Admission Criteria	none	16.2__2.1
Blind Broken	none	16.2__1.3
Urine Drug Screen	none	16.2__2.2
Hepatitis Screen	none	16.2__2.3
Pregnancy Test Results	none	16.2__2.4
Other Medications and Supplements	none	16.2__7.3

In reviewing the data for all subjects, deviations from the protocol were identified. Clinically significant inclusion/exclusion criteria deviations included the following: failure to perform a pregnancy test at the Baseline Visit (19 subjects), current or expected use of an exclusionary medication (10 subjects), failure to have an average of ≥ 4 points on the diary-based Pain Rating Scale during the Baseline Pain Assessment Phase and ≥ 4 points on the site-based Pain Rating Scale at the Baseline Visit (6 subjects), acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness (2 subjects), and failure to have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy (2 subjects). These and other minor deviations were not considered important enough to affect the outcome of the study.

One hundred twenty (15 placebo, 30 ABT-594 150 µg, 34 ABT-594 225 µg, and 41 ABT-594 300 µg BID) of the 266 subjects (45%) did not have at least 1 blood sample collected for pharmacokinetic analysis. The remaining 146 subjects (55%) had at least 1 blood sample collected. At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

Study drug dosing errors were noted for 3 subjects. At the Baseline Visit, Primer Phase modules 17011 and 17001 were incorrectly dispensed to Subjects 4136 (placebo) and 4134 (ABT-594 150 µg BID), respectively. These subjects took incorrect study drug on Study Days 1 through 7. The subjects were also dispensed Treatment Phase modules at the same visit and these modules were dispensed correctly. Therefore, subjects 4136 and 4134 were each taking their correct randomized dose beginning on Study Day 8. One subject (4099) randomized to ABT-594 225 µg BID actually received ABT-594 300 µg BID (module 30157) on Study Days 21 through 37 (Appendix 16.2__5.1.1). In all efficacy and safety analyses, data for Subject 4099 were included in the ABT-594 225 µg BID treatment group.

11.0 Efficacy and Pharmacokinetic Evaluation

11.1 Data Sets Analyzed

The 266 randomized subjects who received at least 1 dose of study drug comprise the "all treated subjects" dataset and are included in the safety analyses. The primary efficacy dataset was the ITT dataset, which included all randomized subjects who took at least 1 dose of study drug and had at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale). Of the 266 all treated subjects, 251 were included in the ITT dataset (Tables 14.2__1.1 and 14.2__1.2).

In addition, efficacy analyses based on "evaluable" and "completers" data were performed. The 217 subjects who received at least 7 days of study drug and who had at least 1 pre-dose pain assessment and at least 1 post-Day 7 pain assessment for the diary-based Pain Rating Scale comprised the "evaluable" efficacy dataset (Tables 14.2__8.1 and 14.2__8.2). The 138 subjects who did not prematurely discontinue from the study for any reason were included in the completers data set. Efficacy ITT, evaluable, and completer exclusions are identified in the data listings.

The treatment groups were similar with respect to the number and percentage of subjects contributed by each investigator in the ITT and evaluable datasets (Table 14.1__1.2).

A summary of subject accountability is presented in Table 11.1a.

Table 11.1a Disposition of Subjects by Dataset

	Treatment Group			
		ABT-594		
	Placebo	150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
Number of Subjects Randomized	65	65	69	67
Subjects Included in the All Treated Subjects Dataset	65	65	69	67
Subjects Included in the Intent-to-Treat Dataset	62	61	66	62
Subjects Included in the Efficacy Evaluable Dataset	61	53	54	49
Subjects Included in the Completers Dataset	51	40	30	17

Cross Reference: Table 14.1__1.2 and Appendices 16.2__3.1, 16.2__3.2, and 16.2__3.3

11.2 Demographic and Other Baseline Characteristics

All demographic and other baseline characteristic results are for all treated subjects, unless otherwise specified. The location of demographic and other baseline characteristic data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Demographics	14.1__4.1	16.2__4.1
Medical History	14.1__5.1 14.1__5.2	16.2__4.2
Nicotine Consumption	14.1__4.1	16.2__4.3
Baseline Pain Assessments	14.1__6	16.2__6.2.1 16.2__6.2.2 16.2__6.3.1 16.2__6.3.2 16.2__6.4.1 16.2__6.4.2 16.2__6.4.3

11.2.1 Demographics

No statistically significant differences were observed among treatment groups for sex, race, age, height, or weight. The average age was 61.9 years (range = 20 - 86 years). Eighty-nine percent of the subjects were white. Subject demographic characteristics are presented in Table 11.2a.

Table 11.2a Demographic Characteristics (All Treated Subjects)

Demographic Characteristic	Treatment Group n (%)				p-value[a]
		ABT-594			
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)	
Sex					0.870
Female	27 (42%)	31 (48%)	33 (48%)	30 (45%)	
Male	38 (58%)	34 (52%)	36 (52%)	37 (55%)	
Race[b]					0.751
White	57 (88%)	58 (89%)	64 (93%)	59 (88%)	
Black	7 (11%)	6 (9%)	3 (4%)	8 (12%)	
Asian	0	1 (2%)	1 (1%)	0	
Native American	0	0	1 (1%)	0	
Other	1 (2%)	0	0	0	
Age (years)					0.110
Mean (SD)	60.2 (11.43)	60.8 (10.78)	61.8 (11.80)	64.7 (11.10)	
Min-Max	20 - 80	36 - 85	24 - 84	31 - 86	
Height (inches)[c]	(N=65)	(N=65)	(N=69)	(N=66)	0.300
Mean (SD)	68.4 (4.47)	67.5 (3.93)	67.1 (4.27)	67.3 (3.73)	
Min-Max	60 - 77	59 - 75	59 - 79	60 - 75	
Weight (pounds)[c]					0.758
Mean (SD)	205.3 (36.44)	200.0 (40.03)	199.2 (34.57)	203.1 (34.94)	
Min-Max	127.9 - 275.0	113.0 - 276.0	112.0 - 258.0	134.5 - 277.8	

a p-values are from extension of Fisher's exact test comparing treatment groups (sex, race), or a 1-way ANOVA model comparing treatment groups (age, height, and weight).
b Non-white races were combined for calculation of p-value. American Indian/Alaska Native was represented as Native American.
c At baseline.

Cross Reference: Table 14.1__4.1 and Appendix 16.2__4.1

11.2.2 Other Baseline Characteristics

There were no statistically significant differences among treatment groups in the ITT analysis with respect to all pain assessment variables (including diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score) and other baseline characteristics including nicotine use. The baseline characteristics for the ITT dataset are presented in Table 11.2b.

Pain assessment scales are presented in Appendix 16.1.13.

Table 11.2b Other Baseline Characteristics (Intent-to-Treat Dataset)

Baseline Characteristic	Treatment Group				p-value[a]
		ABT-594			
	Placebo	150 µg BID	225 µg BID	300 µg BID	
Diary-Based Pain Scale[b]	(N=62)	(N=64)	(N=67)	(N=66)	0.847
Baseline Mean (SD)	6.5 (1.43)	6.6 (1.69)	6.7 (1.51)	6.7 (1.74)	
Site-Based Pain Scale[b]	(N=64)	(N=64)	(N=69)	(N=66)	0.608
Baseline Mean (SD)	6.5 (1.67)	6.7 (1.98)	6.7 (1.57)	6.9 (1.91)	
Neuropathic Pain Scale Total Score[c]	(N=64)	(N=65)	(N=69)	(N=64)	0.910
Baseline Mean (SD)	56.5 (17.47)	55.1 (17.47)	56.3 (15.18)	57.3 (19.81)	
Nicotine Used[d]	(N=65)	(N=65)	(N=69)	(N=67)	0.098
Former User	29 (45%)	24 (37%)	18 (26%)	25 (37%)	
Non-User	32 (49%)	31 (48%)	40 (58%)	38 (57%)	
Current User	4 (6%)	10 (15%)	11 (16%)	4 (6%)	

a p-values are from extension of Fisher's exact test comparing treatment groups (nicotine use) or 1-way ANOVA model comparing treatment groups (pain scores).
b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
c Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most.
d Former users and non-users were combined for calculation of p-value.

Cross Reference: Tables 14.1__4.1, 14.1__6 and Appendices 16.2__4.3, 16.2__6.2.1, 16.2__6.2.2, 16.2__6.3.1, 16.2__6.4.1, 16.2__6.4.2, and 16.2__6.4.3

A medical history was obtained for each subject who entered the study. Among currently symptomatic subjects, sporadic statistically significant differences were observed between each of the ABT-594 150 µg BID and 300 µg BID treatment groups and the placebo

treatment group for the proportions of subjects who had a specific condition/diagnosis (Table 14.1__5.1). Among currently asymptomatic subjects, no apparent differences were observed between treatment groups for the proportion of subjects with a specific condition/diagnosis (Table 14.1__5.2).

11.2.3 Concurrent Medication Use

The proportion of subjects using a concomitant medication during the study was similar among treatment groups. The number and proportion of subjects who took concomitant medications during the study and listing of subject numbers by therapeutic classifications are presented in Tables 14.1__7.1 and 14.1__7.2, respectively. Individual subject data listings for subjects who took previous and concomitant medications are presented in Appendix 16.2__7.3.

During the Baseline Pain Assessment Phase, no statistically significant difference was observed among treatment groups for the proportion of subjects who used protocol-allowed concomitant analgesic medication (Table 14.2__7.1).

11.3 Measurements of Treatment Compliance

The location of compliance and drug concentration data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Study Drug Administration	14.1__8	16.2__5.1.1 16.2__5.1.2
Plasma Assay	none	16.2__5.3.1 16.2__5.3.2

11.4 Efficacy Evaluations and Tabulations of Individual Subject Data

Each efficacy analysis compared the placebo treatment group versus each of the other ABT-594 treatment groups. Efficacy scale ranges are presented in Appendix 16.1.13.

11.4.1 Efficacy Analyses

The location of efficacy data is presented below.

Assessment	Statistical Analyses Tables[a]	Individual Subject Listing Appendix
Diary-Based Pain Rating Scale	14.2__2.1.1.1 14.2__2.1.1.2 14.2__2.1.2 14.2__2.1.3 14.2__2.1.4 14.2__2.2 14.2__2.3 14.2__2.4.1.1 14.2__2.4.1.2 14.2__2.4.2 14.2__2.4.3 14.2__2.4.4	16.2__6.2.1
Site-Based Pain Rating Scale	14.2__3.1.1 14.2__3.1.2 14.2__3.1.3 14.2__3.2 14.2__3.3 14.2__3.4	16.2__6.2.2
Neuropathic Pain Scale	14.2__4.1.1 14.2__4.1.2 14.2__4.1.3 14.2__4.1.4 14.2__4.2 14.2__4.3 14.2__4.4	16.2__6.3.1 16.2__6.3.2
Global Impression of Change	14.2__5.1 14.2__5.2 14.2__5.3 14.2__5.4	16.2__6.5
SF-36™ Health Status Survey	14.2__6	16.2__6.4.1 16.2__6.4.2 16.2__6.4.3
Concomitant Analgesic Medication Use	14.2__7.1 14.2__7.2 14.2__7.3	16.2__7.4

a Statistical analyses tables for the ITT dataset.

Analyses were performed on the ITT, evaluable, and study completers datasets using both the LOCF and OC methods; the ITT dataset was the protocol-defined primary dataset. Efficacy results are presented only for the ITT dataset. Efficacy results for the evaluable and study completers dataset were generally similar to those for the ITT dataset (Tables 14.2__8.1 through 14.2__13 and 14.2__14.1.1.1 through 14.2__18, respectively). Furthermore, results from analyses that used the OC method were generally similar to those that used the LOCF method, and differences are noted between the 2 methods.

11.4.1.1 Primary Efficacy Variable

Diary-Based Pain Rating Scale Scores at Final Evaluation

The mean improvement from baseline to final for the average diary-based Pain Rating Scale scores was statistically significantly greater for each of the ABT-594 treatment groups compared to placebo. A summary of the mean change from baseline to final for the average diary-based Pain Rating Scale scores is presented in Table 11.4a.

Table 11.4a Summary of the Analysis of Mean Change From Baseline[a] to Final[b] for the Average Diary-Based Pain Rating Scale[c] Scores Using LOCF Method (Intent-to-Treat Dataset)

	Treatment Group			
		ABT-594		
	Placebo (N=58)	150 µg BID (N=56)	225 µg BID (N=58)	300 µg BID (N=53)
Baseline Visit Model-Based Mean (SE)[d]	6.5 (0.21)	6.6 (0.22)	6.7 (0.21)	6.7 (0.22)
Change to Final Model-Based Mean (SE)[d]	-1.1 (0.29)	-1.9 (0.30)*	-1.9 (0.29)*	-2.0 (0.30)*

SE = standard error.
a Average of the last 7 pain scores prior to Day 1 of the study.
b Average of the values from the last 7 days on study drug.
c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
d Least square means from 2-way ANOVA without interaction.
* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__2.1.1.1 and 14.2__2.1.1.2 and Appendix 16.2__6.2.1

A statistically significant linear dose response was observed for mean change from baseline to final for the average diary-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__2.3).

11.4.1.2 Secondary Efficacy Variables

Change From Baseline to Final

The mean improvement from baseline to final for the average site-based Pain Rating Scale scores was statistically significantly greater in each of the ABT-594 treatment groups compared to placebo.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. However, sporadic statistically significant differences were observed between placebo and 1 of the ABT-594 treatment groups for the mean change from baseline to final in the following items from the Neuropathic Pain Scale: intense, dull, and deep pain (Table 14.2__4.1.2).

In the analysis of the mean change from baseline to final in the SF-36™ Health Status Survey, a statistically significant difference was observed between the ABT-594 225 µg BID and placebo treatment groups in the physical component summary. Subjects in the ABT-594 225 µg BID treatment group showed a greater improvement from baseline compared to subjects in the placebo treatment group. Additionally, a statistically significant difference was observed between the ABT-594 300 µg BID and placebo treatment groups in the mental component summary. Subjects in the placebo treatment group showed an improvement from baseline, while subjects in the ABT-594 300 µg BID treatment group showed a deterioration from baseline. There were no other statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the SF-36™ Health Status Survey subscales.

A summary of the mean change from baseline to final for secondary efficacy variables is presented in Table 11.4b.

Table 11.4b Change from Baseline to Final for Secondary Efficacy Variables[a] Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
		ABT-594		
	Placebo	150 µg BID	225 µg BID	300 µg BID
Average Site-Based Pain Rating Scale[b] Scores	(N=57)	(N=47)	(N=40)	(N=29)
Baseline Visit Model-Based Mean (SE)[c]	6.4 (0.25)	6.7 (0.27)	6.4 (0.30)	6.7 (0.34)
Change to Final Model-Based Mean (SE)[c]	-1.1 (0.36)	-2.7 (0.39)*	-2.1 (0.43)*	-2.8 (0.49)*
Neuropathic Pain Scale[d] Total Score	(N=57)	(N=48)	(N=40)	(N=29)
Baseline Visit Model-Based Mean (SE)[c]	54.3 (2.32)	54.6 (2.55)	53.5 (2.82)	56.3 (3.16)
Change to Final Model-Based Mean (SE)[c]	-11.4 (3.04)	-16.1 (3.34)	-15.8 (3.69)	-19.7 (4.14)
SF-36™ Health Status Survey Physical Component[e]	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit Model-Based Mean (SE)[c]	35.0 (1.29)	32.7 (1.36)	32.7 (1.28)	34.3 (1.31)
Change to Final Model-Based Mean (SE)[c]	0.6 (0.97)	3.2 (1.02)	3.3 (0.96)*	0.7 (0.98)
SF-36™ Health Status Survey Mental Component[e]	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit Model-Based Mean (SE)[c]	47.9 (1.50)	50.5 (1.59)	50.6 (1.49)	49.6 (1.52)
Change to Final Model-Based Mean (SE)[c]	1.7 (1.29)	-0.9 (1.35)	-1.3 (1.27)	-1.9 (1.30)*

NOTE: Due to the number of subjects who dropped out or failed to complete certain efficacy assessments, the number of subjects included in each of the secondary efficacy analyses was smaller than that of the primary analyses.

a Pain assessment scales are presented in Appendix 16.1.13.

b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

c Values represent model-based means (SE) which are least square means from 2-way ANOVA without interaction.

d Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most for each of the 10 items.

e Results based on transformed scores as calculated using SF-36™ health survey manual and interpretation guide.

* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__3.1.1, 14.2__4.1.1, and 14.2__6 and Appendices 16.2__6.2.2, 16.2__6.3.1, 16.2__6.4.1, and 16.2__6.4.2

Global Impression of Change

No statistically significant differences were observed between the placebo and each of the ABT-594 treatment groups in the mean overall change from baseline in the subject and clinician global impression of change. However, each of the ABT-594 treatment groups was numerically better than placebo. A summary of the mean change from baseline to final for subject and clinician global impression of change is presented in Table 11.4c.

Table 11.4c Change from Baseline to Final for Subject and Clinician Global Impression of Change[a] Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
		ABT-594		
	Placebo	150 µg BID	225 µg BID	300 µg BID
Subject Global Impression of Change[b]	(N=61)	(N=59)	(N=61)	(N=59)
Univariate Mean Change (SE)[c]	0.8 (0.18)	0.8 (0.21)	1.3 (0.21)	1.1 (0.19)
Clinician Global Impression of Change[b]	(N=61)	(N=59)	(N=60)	(N=59)
Univariate Mean Change (SE)[c]	0.7 (0.17)	0.8 (0.21)	1.2 (0.18)	1.1 (0.18)

a Pain assessment scales are presented in Appendix 16.1.13.
b Overall change defined as follows: 3 = much improved, 2 = moderately improved, 1 = minimally improved, 0 = no change, -1 = minimally worse, -2 = moderately worse, -3 = much worse.
c Values represent univariate means (SE) for the Cochran-Mantel-Haenszel test.

Cross Reference: Table 14.2__5.3 and Appendix 16.2__6.5

In the distribution analyses of subject and clinician global impression of change (much, moderately, or minimally improved, no change, or much, moderately, or minimally worse) statistically significant differences from placebo were observed for the ABT-594 225 µg BID treatment group (Table 14.2__5.1). When responses were further categorized as improved (including much, moderate, or minimal), no change,

or worsened (including much, moderate, or minimal), there was a statistically significant difference between the ABT-594 225 µg BID and placebo treatment groups for clinician global impression of change. Based on the clinician's assessment, a greater proportion of subjects in the ABT-594 225 µg BID treatment group were improved (63%) compared to subjects in the placebo treatment group (42%; Table 14.2__5.2).

Dose Response

A statistically significant linear dose response was observed for mean change from baseline to final for the average site-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__3.3). No statistically significant linear dose response was observed for mean change from baseline to final for the Neuropathic Pain Scale Total Score, regardless of whether the model included or excluded the placebo treatment group (Table 14.2__4.3).

Change From Baseline to Each Week - Diary-Based Pain Rating Scale

Improvements from baseline were seen in diary-based Pain Rating Scale scores at each week for all treatment groups. In the LOCF analyses, the ABT-594 150 µg BID treatment group had statistically significantly greater mean improvements from baseline to Weeks 5, 6, and 7 for the average diary-based Pain Rating Scale scores when compared to placebo. No statistically significant differences were observed between the ABT-594 225 µg BID and placebo treatment groups at any time point. The mean improvements from baseline to Weeks 3, 4, 5, and 7 for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo. Results of OC analyses were generally similar to those of LOCF analyses, with a more consistent treatment effect observed in the OC analyses. A summary of the mean change from baseline to each week for the average diary-based Pain Rating Scale scores is presented in Table 11.4d.

Table 11.4d Summary of the Analysis of Mean Change From Baseline[a] to Each Week for the Average Diary-Based Pain Rating Scale[b] Scores Using LOCF and OC Methods (Intent-to-Treat Dataset)

	Treatment Group							
	Placebo		ABT-594					
			150 µg BID		225 µg BID		300 µg BID	
	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
Visit	(N=58)	(N=[c])	(N=56)	(N=[c])	(N=58)	(N=[c])	(N=53)	(N=[c])
Baseline Mean[d]	6.5	6.5[e]	6.6	6.6	6.7	6.7	6.7	6.7
Week 1[d]	-0.6[f]	-0.6	-0.8	-0.8	-0.8	-0.8	-0.7	-0.7
Week 2[d]	-1.0[f]	-1.0	-1.1	-1.1	-1.2	-1.3	-1.4	-1.8*
Week 3[d]	-1.0	-0.9	-1.2	-1.4	-1.5	-2.0*	-1.7*	-2.4*
Week 4[d]	-1.1	-1.1	-1.6	-1.9*	-1.5	-2.3*	-1.9*	-2.4*
Week 5[d]	-1.0	-1.0	-1.8*	-2.3*	-1.7	-2.5*	-1.9*	-2.9*
Week 6[d]	-1.1	-1.1	-1.9*	-2.4*	-1.7	-2.6*	-1.8	-2.8*
Week 7[d]	-1.1	-1.0	-1.9*	-2.4*	-1.8	-2.6*	-1.9*	-3.1*

LOCF = last observation carried forward; OC = observed cases.
Note: All values represent model-based means.
a Average of the last 7 pain scores prior to Day 1 of the study.
b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
c No's for observed cases analyses:

	Placebo	ABT-594 150 µg BID	ABT-594 225 µg BID	ABT-594 300 µg BID
Week 1	57	56	58	53
Week 2	56	49	44	38
Week 3	56	47	37	27
Week 4	52	44	34	23
Week 5	50	39	33	20
Week 6	50	39	30	17
Week 7	49	38	29	17

d Least square means from 2-way ANOVA without interaction.
e N = 58 at baseline.
f N = 57 at Weeks 1 and 2.
* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__2.1.3 and 14.2__2.4.3 and Appendix 16.2__6.2.1

Change From Baseline to Each Visit - Diary-Based Pain Rating Scale

Each treatment group showed improvement from baseline to the 7-day average prior to each visit in diary-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits III and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 μg BID and 225 μg BID treatment groups compared to placebo. Furthermore, the mean changes from baseline to Treatment Visits II, III, and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 μg BID treatment group compared to placebo (Table 14.2__2.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__2.4.2).

Change From Baseline to Each Visit - Site-Based Pain Rating Scale

Each treatment group showed improvement from baseline to each visit in site-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits II, III, and IV for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 μg BID treatment group compared to placebo. The mean change from baseline to Treatment Visit IV for the average site-based Pain Rating Scale score was statistically significantly greater in the ABT-594 225 μg BID treatment group compared to placebo. The mean changes from baseline to each Treatment Visit for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 μg BID treatment group compared to placebo (Table 14.2__3.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__3.4).

11.4.1.3 Other Efficacy Variables

Proportion of Responders

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to the final evaluation, was analyzed for the following efficacy variables: average diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either the diary- or site-based average Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group. A summary of the proportion of subjects with a positive response to study drug as measured by average diary- and site-based Pain Rating Scale scores is presented in Table 11.4e.

Table 11.4e Proportion of Subjects Responding[a] to Treatment as Measured by Diary- and Site-Based Pain Rating Scale Scores[b] Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
		ABT-594		
	Placebo	150 µg BID	225 µg BID	300 µg BID
Average Diary-Based Pain Rating Scale[c] Scores	(N=58) 12%	(N=56) 27%*	(N=58) 26%	(N=53) 26%*
Average Site-Based Pain Rating Scale[c] Scores	(N=57) 14%	(N=47) 40%*	(N=40) 35%*	(N=29) 48%*

a Defined as a 50% or greater improvement from baseline to the final evaluation.
b Pain assessment scales are presented in Appendix 16.1.13.
c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__2.1.4 and 14.2__3.1.3 and Appendices 16.2__6.2.1 and 16.2__6.2.2

Concomitant Analgesic Medication Use

No statistically significant differences were observed among the treatment groups for the proportion of subjects using any analgesic medication or within 24 hours of analgesic medication at each visit during the Treatment Phase and over the entire Treatment Phase (Tables 14.2__7.1 and 14.2__7.2). There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the number of times analgesic medication was used (Table 14.2__7.3).

11.4.2 Statistical and Analytical Issues

11.4.2.1 Adjustments for Covariates

Adjustments for covariates, including sex, race, age, and weight, were not performed in the efficacy analyses.

11.4.2.2 Handling of Dropouts or Missing Data

Two sets of efficacy analyses, corresponding to the handling of missing data, were performed. The LOCF analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had a value for each specified evaluation. This technique was intended to reduce bias caused by subjects who prematurely discontinued due to lack of efficacy. The OC method did not estimate missing evaluations and a subject who did not have a pain evaluation on a scheduled visit was excluded from the OC analysis for that visit. Results obtained with the OC method were generally consistent with those obtained with the LOCF method.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed.

11.4.2.4 Multicenter Studies

This was a multicenter study. The treatment-by-center interaction was not statistically significant at an α=0.10 in the analysis of change from baseline to the final evaluation for the diary-based Pain Rating Scale scores (Table 14.2__2.2), indicating homogeneity of treatment effects across centers for the primary endpoint. Therefore, the treatment-by-center interaction term was not used in the primary or secondary analyses. Additionally, since the treatment-by-center interaction term was not used in the primary analysis, data from study centers with less than 1 subject per treatment group in the ITT dataset, were not combined for the analyses.

11.4.2.5 Multiple Comparisons/Multiplicity

No statistical adjustments were made for multiple comparisons.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

Subjects who received less than 7 days of study drug or who had no baseline or post Day 7 pain assessment for the diary-based Pain Rating Scale were identified prior to breaking the blind and were excluded from the evaluable dataset. Results for ITT and evaluable datasets were similar.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

The study was not designed to assess equivalence to an active control.

11.4.2.8 Examination of Subgroups

Subgroup analyses for potentially influential factors were not performed.

11.4.3 Tabulation of Individual Response Data

There were no tabulations of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.4 Drug Dose, Drug Concentration, and Relationship to Response

Blood samples for ABT-594 plasma assay were to be collected for all subjects at Treatment Visits I and IV. For those subjects participating in the pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), additional blood samples were collected at Treatment Visits I and IV. Plasma concentrations of ABT-594 are listed for each subject in Appendix 16.2__5.3.1.

A complete discussion of the pharmacokinetic variables analyzed will be presented in a separate Clinical Pharmacokinetic Report.

11.4.5 Drug-Drug and Drug-Disease Interactions

Analyses which examined drug-drug and drug-disease interactions were not performed.

11.4.6 By-Subject Displays

There were no by-subject displays of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.7 Efficacy Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

11.5 Pharmacokinetic Variables

Complete pharmacokinetic results will be presented in a separate Clinical Pharmacokinetic Report.

12.0 Safety Evaluation

All 266 randomized subjects who were treated with study drug (65 placebo, 65 ABT-594 150 µg, 69 ABT-594 225 µg, and 67 ABT-594 300 µg BID) were evaluated for safety. Adverse events, clinical laboratory data, vital signs (including weight), and 12-lead ECG data were used to evaluate safety.

12.1 Extent of Exposure

The mean duration of treatment was statistically significantly different among treatment groups. The placebo treatment group received study drug for a mean 44.3 days, as compared to 35.9, 28.6, and 22.7 days for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups, respectively. A summary of the extent of exposure to study drug is presented in Table 12.1a.

Table 12.1a Extent of Exposure

Duration of Treatment (Days)	Treatment Group n (%)			
		ABT-594		
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
<7	1 (2%)	8 (12%)	14 (20%)	12 (18%)
7 - 13	2 (3%)	5 (8%)	14 (20%)	19 (28%)
14 - 20	4 (6%)	4 (6%)	4 (6%)	6 (9%)
21 - 27	5 (8%)	6 (9%)	3 (4%)	8 (12%)
28 - 34	0	2 (3%)	0	3 (4%)
35 - 41	1 (2%)	0	4 (6%)	2 (3%)
42 - 48	3 (5%)	5 (8%)	3 (4%)	1 (1%)
≥49	49 (75%)	35 (54%)	27 (39%)	16 (24%)
Mean (SD)*	44.3 (13.5)	35.9 (19.1)	28.6 (20.5)	22.7 (18.0)

Note: Percentages may not sum to 100 due to rounding.
SD = standard deviation.
* Statistically significant difference among treatment groups ($p \leq 0.05$).

Cross Reference: Table 14.1__8 and Appendix 16.2__5.1.1

12.2 Adverse Events

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Adverse Events		16.2__7.1.1
All Treatment-Emergent	14.3.1__1.1	
by Severity	14.3.1__1.2.1	
	14.3.1__1.2.2	
by Relationship to Study Drug	14.3.1__1.3.1	
	14.3.1__1.3.2	
Incidence Across Time	14.3.1__2.1	
Prevalence Across Time	14.3.1__2.2	
Identification of Subjects	14.3.1__3.1	
Medical Terms and Descriptions Associated with Each COSTART Term	14.3.1__3.2	

12.2.1 Brief Summary of Adverse Events

Among all treated subjects, 66% of subjects who received placebo and 83%, 90%, and 91% of subjects who received ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and

300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, vomiting, dizziness, abnormal dreams, and headache.

12.2.2 Display of Adverse Events

A summary of the treatment-emergent adverse events occurring in ≥10% of subjects in any ABT-594 treatment group is presented by the investigator's assessment of relationship to study drug in Table 12.2a.

Table 12.2a Summary of Most Frequently Reported[a] Treatment-Emergent Adverse Events By Relationship to Study Drug

	Treatment Group n (%)																					
	Placebo (N=65)						ABT-594															
							150 µg BID (N=65)						225 µg BID (N=69)						300 µg BID (N=67)			
	Relationship[b]				Total		Relationship[b]				Total		Relationship[b]				Total		Relationship[b]				Total	
COSTART Term	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%
Any Event					43	66%					54	83%*					62	90%*					61	91%*
Nausea	0	0	2	5	7	11%	0	1	5	16	22	34%*	1	0	5	24	30	43%*	1	0	3	27	31	46%*
Dizziness	1	1	0	1	3	5%	0	1	2	8	11	17%*	0	3	3	18	24	35%*	0	0	3	17	20	30%*
Vomiting	0	0	1	1	2	3%	0	0	1	9	10	15%*	1	0	3	13	17	25%*	1	1	1	11	14	21%*
Abnormal Dreams	0	0	0	0	0		0	0	2	12	14	22%*	0	0	1	14	15	22%*	0	0	2	10	12	18%*
Headache	2	2	3	1	8	12%	3	3	3	4	13	20%	2	2	0	6	10	14%	1	0	1	11	13	19%
Asthenia	0	0	0	1	1	2%	0	0	3	1	4	6%	0	0	3	8	11	16%*	0	1	2	11	14	21%*
Diarrhea	0	0	0	2	2	3%	1	2	2	2	7	11%	2	0	2	4	8	12%	1	1	0	2	4	6%
Dyspepsia	0	0	2	0	2	3%	0	0	3	2	5	8%	0	0	0	8	8	12%	0	0	1	4	5	7%
Insomnia	0	1	2	0	3	5%	0	0	1	0	1	2%	1	1	2	5	9	13%	0	0	2	5	7	10%

NR = not related; PN = probably not related; PO = possibly related; PR = probably related.

a Adverse events occurring in ≥10% of subjects in any ABT-594 treatment group.

b As assessed by the investigator.

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.3.1_1.1, 14.3.1__1.3.1 and 14.3.1__1.3.2 and Appendix 16.2__7.1.1

Most adverse events in all treatment groups were mild or moderate in severity and were considered by the investigator to be possibly or probably related to study drug (Tables 14.3.1__1.2.1, 14.3.1__1.2.2, 14.3.1__1.3.1, and 14.3.1__1.3.2).

12.2.3 Analysis of Adverse Events

The overall incidence of treatment-emergent adverse events was statistically significantly higher for subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (83%, 90%, and 91%, respectively) than for subjects in the placebo treatment group (66%). Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). No other statistically significant treatment differences were observed for any specific treatment-emergent adverse event (Table 14.3.1__1.1).

Five percent (3/65) of placebo-treated subjects, 11% (7/65) of ABT-594 150 µg-treated subjects, 12% (8/69) of ABT-594 225 µg-treated subjects, and 12% (8/67) of ABT-594 300 µg BID-treated subjects experienced at least 1 severe adverse event, most of which were considered probably related to study drug by the investigator. The remaining adverse events were mild or moderate in severity. A summary of the severity of treatment-emergent adverse events grouped by body system and COSTART term is presented in Tables 14.3.1__1.2.1 and 14.3.1__1.2.2.

12.2.4 Listing of Adverse Events by Subject

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Treatment-Emergent Adverse Events Grouped by Body System, COSTART Term, Medical Term, and Description With Subject Number Identification (All Treated Subjects)	14.3.1__3.1	16.2__7.1.1
Adverse Event Medical Terms and Descriptions	14.3.1__3.2	

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The location of deaths, other serious adverse events, and other significant adverse event data is presented below.

Assessment	Statistical Analyses Tables	Narrative Section	Individual Subject Listing Appendix
Deaths	14.3.2__1.1	14.3.3	16.2__7.2
Serious Adverse Events	14.3.2__1.2	14.3.3	16.2__7.1.2
Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued	14.3.2__2	14.3.3	16.2__7.1.1
Number and Percentage of Subjects With Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued Grouped by Body System and COSTART Term	14.3.2__3		16.2__7.1.1

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug.

A listing of subjects who died during the course of the study is presented in Appendix 16.2__7.2.

12.3.1.2 Other Serious Adverse Events

In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported a serious adverse event during the study (Table 14.3.2__1.2). One of these subjects reported an event (palpitation reported in an ABT-594 300 µg BID-treated subject) considered probably related to study drug. The event was a single occurrence and resolved within 90 minutes. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

Eight subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each of these subjects had multiple risk factors for cardiovascular disease. Subjects reporting serious adverse events (including death) during the study are presented in Table 12.3a.

Table 12.3a Subjects Reporting Serious Adverse Events During the Study

Treatment Group	Investigator/ Subject	Age (yrs)/ Sex	Day of Onset[a]	Day of Resolution[a]	COSTART Term - Reason Serious[b]	Relationship to Study Drug
Placebo	DeBold/4053	52/F	52 (2)	53 (3)	Gastroenteritis - HO	Not related
			52 (2)	53 (3)	Dehydration - HO	Not related
			52 (2)	53 (3)	Ketosis - HO	Not related
	Singer/4401	53/M	34	42 (1)	Angina Pectoris[c] - HO	Not related
			49 (9)	unknown	Atrial Fibrillation - HO	Not related
	Weinstein/4027	65/F	9 (1)	12 (4)	Cerebrovascular Accident[c] - HO	Probably not
ABT-594 150 µg BID	Baumel/4149	71/M	65 (15)	66 (16)	Angina Pectoris - HO	Not related
			65 (15)	66 (16)	Myocardial Infarct - HO	Not related
	Fried/4083	66/F	15 (1)	17 (3)[d]	Syncope[c] - HO	Not related
			15 (1)	22 (3)[d]	Atrial Fibrillation[c] - HO	Not related
	Kipnes/4070	48/F	10	12	Pain[c] - HO	Not related
	Singer/4412	57/M	36	50	Peripheral Vascular Disorder - HO	Not related
	Storey/4100[e]	56/F	79 (58)[f]	79 (58)	Suicide Attempt - DEA	Not related
ABT-594 225 µg BID	Kluge/4133	66/M	6	9	Gastrointestinal Disorder[c] - HO	Not related
	Shaibani/4451	60/F	18	18	Dyspnea[c] - HO	Probably not
			18	20 (2)	Angina Pectoris[c] - HO	Probably not
ABT-594 300 µg BID	Drucker/4002	70/M	4	4	Palpitation[c] - HO	Probably
	Holmlund/4193[e]	55/M	40 (32)[f]	64 (56)	Accidental Injury[g] - HO	Not related
	Holmlund/4197	62/F	5	6 (1)	Angina Pectoris[c] - HO	Not related
	Weinstein/4031	80/M	43 (7)	80 (44)[d]	Cellulitis[c] - HO	Not related

M = male, F = female.
a Number in parentheses represents the number of days after the last dose of study drug.
b HO=hospitalization; DEA=death.
c Adverse event leading to premature discontinuation.
d Adverse event was ongoing as of this day.
e Subject prematurely discontinued due to another adverse event.
f Adverse event onset >30 days after the last dose of study drug.
g Described as status post fall down stairs.

Cross Reference: Table 14.3.2__1.2 and Appendices 16.2.__7.1.1 and 16.2__7.1.2

A listing of all subjects who experienced serious adverse events during the study is presented by treatment group and subject number in Table 14.3.2__1.2.

12.3.1.3 Other Significant Adverse Events

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

A summary of adverse events leading to premature discontinuation of study drug is presented by treatment group in Table 12.3b.

Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects)

	Treatment Group n (%)			
		ABT-594		
COSTART Term	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Any Event[a]	6 (9%)	18 (28%)*	32 (46%)*	44 (66%)*
Nausea	1 (2%)	8 (12%)*	15 (22%)*	20 (30%)*
Dizziness	0	4 (6%)	11 (16%)*	13 (19%)*
Vomiting	0	4 (6%)	10 (14%)*	12 (18%)*
Abnormal Dreams	0	3 (5%)	6 (9%)*	7 (10%)*
Headache	0	1 (2%)	3 (4%)	8 (12%)*
Insomnia	0	1 (2%)	5 (7%)	4 (6%)
Asthenia	0	0	3 (4%)	6 (9%)*
Dyspepsia	0	2 (3%)	4 (6%)	3 (4%)
Diarrhea	0	0	4 (6%)	2 (3%)
Pain	0	1 (2%)	1 (1%)	4 (6%)
Sweating	0	1 (2%)	2 (3%)	2 (3%)
Chills	0	0	2 (3%)	2 (3%)
Flatulence	1 (2%)	0	1 (1%)	2 (3%)
Hypertension	0	0	2 (3%)	2 (3%)
Nervousness	0	0	3 (4%)	1 (1%)
Abdominal Pain	0	0	1 (1%)	2 (3%)
Angina Pectoris	1 (2%)	0	1 (1%)	1 (1%)
Chest Pain	0	0	1 (1%)	2 (3%)
Dyspnea	0	0	1 (1%)	2 (3%)
Palpitation	0	0	1 (1%)	2 (3%)
Taste Perversion	0	2 (3%)	0	1 (1%)
Abnormal Gait	0	0	2 (3%)	0
Accidental Injury	1 (2%)	0	0	1 (1%)
Amblyopia	0	1 (2%)	1 (1%)	0
Anorexia	0	0	1 (1%)	1 (1%)
Confusion	0	0	1 (1%)	1 (1%)
Hallucinations	0	0	2 (3%)	0
Malaise	0	0	1 (1%)	1 (1%)
Paresthesia	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	1 (1%)
Thinking Abnormal	0	0	0	2 (3%)
Abdomen Enlarged	0	0	0	1 (1%)
Abnormal Vision	0	0	0	1 (1%)
Alopecia	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Arthralgia	0	0	1 (1%)	0
Ataxia	0	0	1 (1%)	0
Atrial Fibrillation	0	1 (2%)	0	0
Back Pain	0	0	0	1 (1%)

a Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects; continued)

COSTART Term	Treatment Group n (%)			
		ABT-594		
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Cellulitis	0	0	0	1 (1%)
Cerebrovascular Accident	1 (2%)	0	0	0
Depersonalization	1 (2%)	0	0	0
Depression	0	0	0	1 (1%)
Dry Mouth	0	0	0	1 (1%)
Emotional Lability	0	0	1 (1%)	0
Eructation	0	0	0	1 (1%)
Eye Disorder	0	0	1 (1%)	0
Flu Syndrome	0	0	0	1 (1%)
Gastroenteritis	1 (2%)	0	0	0
Gastrointestinal Disorder	0	0	1 (1%)	0
Glossitis	0	1 (2%)	0	0
Hyperglycemia	0	0	0	1 (1%)
Infection	1 (2%)	0	0	0
Leg Cramps	0	0	0	1 (1%)
Myalgia	0	0	1 (1%)	0
Rash	0	0	0	1 (1%)
Rectal Hemorrhage	0	0	0	1 (1%)
Somnolence	0	1 (2%)	0	0
Stupor	0	0	0	1 (1%)
Syncope	0	1 (2%)	0	0
Tremor	0	0	1 (1%)	0
Vasodilatation	0	0	0	1 (1%)

[a] Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.2__3 and Appendix 16.2__7.1.1

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Narratives for subjects who died, reported a serious adverse event, or prematurely discontinued from the study at least in part to an adverse event are presented in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase (Table 14.3.2__1.1). Subject 4100 died on Day 79 due to a suicide attempt (COSTART term: suicide attempt) that the investigator considered to be unrelated to study drug.

Thirteen subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported 1 or more serious adverse events other than death. However, only 1 of these subjects (ABT-594 300 µg BID) reported an event considered to be probably related to study drug. This subject had a single episode of palpitation (COSTART term: palpitation) on Day 4 that resolved without further incident within 90 minutes. The remaining events were all considered to be not related or probably not related to study drug. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The overall incidence of subjects prematurely discontinuing due to adverse events was statistically significantly higher for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (28%, 46%, and 66%, respectively) than for the placebo treatment group (9%). Statistically significantly higher proportions of subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups prematurely discontinued study drug due to nausea (12%, 22%, and 30%, respectively) compared to subjects in the placebo treatment group (2%). Statistically significantly higher proportions of subjects in the ABT-594 225 µg and 300 µg BID treatment groups prematurely discontinued study drug

due to dizziness (16% and 19%, respectively), vomiting (14% and 18%, respectively), and abnormal dreams (9% and 10%, respectively) compared to subjects in the placebo treatment group (0% each). A statistically significantly higher proportion of subjects in the ABT-594 300 µg BID treatment group prematurely discontinued study drug due to headache (12%) and asthenia (9%) compared to subjects in the placebo treatment group (0% and 0%, respectively).

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

The location of clinical laboratory data is presented below.

Laboratory Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing[a] Appendix
Hematology	14.3.4__1.1 14.3.4__2.1	14.3.4__3.1 14.3.4__4.1	16.2__8.2.1 16.2__8.2.2 16.2__8.2.3 16.2__8.2.4 16.2__8.2.5
Blood Chemistry	14.3.4__1.2 14.3.4__2.2	14.3.4__3.2 14.3.4__4.2	16.2__8.3.1 16.2__8.3.2 16.2__8.3.3 16.2__8.3.4 16.2__8.3.5 16.2__8.3.6
Urinalysis	14.3.4__1.3 14.3.4__2.3	14.3.4__3.3 14.3.4__4.3	16.2__8.4.1 16.2__8.4.2 16.2__8.4.3 16.2__8.4.4 16.2__8.4.5

a Baseline determinations are also presented in Appendix 16.2__4.

Laboratory normal reference ranges are presented in Appendix 16.2__8.1. Criteria for potentially clinically significant laboratory values (i.e., very high or very low values) are presented in Table 14.3.4__1.0.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Hematology

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for hematology parameters is presented in Table 12.4a.

Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters

Hematology Parameter (units)	Treatment Group			
		ABT-594		
	Placebo (N=62)[a]	150 µg BID (N=61)[a]	225 µg BID (N=66)	300 µg BID (N=62)
Hemoglobin (g/dL)				
Baseline Mean	14.10	13.80	13.81	14.02
Mean Change to Minimum	-0.46	-0.30	-0.21*	-0.09*
Hematocrit (%)				
Baseline Mean	40.95	40.39	40.11	40.82
Mean Change to Minimum	-1.06	-1.16	-0.79	-0.26*
Mean Change to Maximum	1.60	0.87	0.73*	0.90
RBC Count (x 10^{12}/L)				
Baseline Mean	4.66	4.61	4.58	4.70
Mean Change to Minimum	-0.13	-0.11	-0.05*	-0.05*
MCV (fL)				
Baseline Mean	88.24	87.79	87.65	87.26
Mean Change to Maximum	2.00	1.26	0.68*	1.24
MCH (pg)				
Baseline Mean	30.52	30.07	30.21	30.00
Mean Change to Minimum	-0.73	-0.30*	-0.33*	-0.27*
Mean Change to Final	-0.29	0.16*	-0.08	0.00
MCHC (g/dL)				
Baseline Mean	34.50	34.30	34.45	34.47
Mean Change to Minimum	-1.08	-0.46*	-0.47*	-0.52*
Platelet Count (x 10^9/L)				
Baseline Mean	246.70	250.27	253.70	241.32
Mean Change to Minimum	-10.98	-13.27	-7.82	4.05*
Mean Change to Maximum	29.33	14.15*	10.89*	26.84
WBC Count (x 10^9/L)				
Baseline Mean	8.01	7.60	7.36	6.95
Mean Change to Minimum	-0.51	-0.50	-0.03*	0.02*
Neutrophils (%)				
Baseline Mean	61.01	62.82	61.86	60.62
Mean Change to Minimum	-2.25	-2.39	-0.60	0.09*
Lymphocytes (%)				
Baseline Mean	30.04	28.78	29.70	30.53
Mean Change to Maximum	2.08	2.17	0.63	0.02*
Eosinophils (%)				
Baseline Mean	2.90	2.32	2.38	2.53
Mean Change to Minimum	-0.82	-0.50	-0.34*	-0.60
Mean Change to Maximum	0.41	0.32	0.29	-0.05*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).
[a] N=60 for Platelet Count only

Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters (continued)

Hematology Parameter (units)	Treatment Group			
		ABT-594		
	Placebo (N=60)	150 µg BID (N=59)	225 µg BID (N=65)	300 µg BID (N=61)
Prothrombin Time (sec)				
Baseline Mean	12.30	12.33	12.20	12.79
Mean Change to Maximum	0.39	0.15	0.08*	0.25
Activated Partial Thromboplastin Time (sec)				
Baseline Mean	24.32	24.69	25.11	25.53
Mean Change to Maximum	1.60	0.72	0.57*	0.27*
Mean Change to Final	0.56	-0.13	-0.24	-0.53*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Blood Chemistry

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for blood chemistry parameters is presented in Table 12.4b.

Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters

Blood Chemistry Parameter (units)	Treatment Group			
		ABT-594		
	Placebo (N=62)	150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Glucose (mg/dL)				
Baseline Mean	175.68	192.13	169.09	183.90
Mean Change to Maximum	57.79	44.36	39.39	17.94*
Total Protein (g/dL)				
Baseline Mean	7.25	7.24	7.31	7.26
Mean Change to Maximum	0.19	0.14	0.03*	0.13
Mean Change to Final	0.03	-0.06	-0.13*	0.00
Total Bilirubin (mg/dL)				
Baseline Mean	0.40	0.43	0.38	0.36
Mean Change to Minimum	-0.05	-0.07	-0.04	-0.00*
Alkaline Phosphatase (IU/L)				
Baseline Mean	75.94	78.74	81.88	74.35
Mean Change to Maximum	4.27	1.43	-0.14*	1.95
SGOT/AST (IU/L)				
Baseline Mean	22.35	21.87	23.70	22.81
Mean Change to Maximum	2.76	1.56	-1.32*	0.84
SGPT/ALT (IU/L)				
Baseline Mean	23.08	24.11	24.65	26.42
Mean Change to Maximum	3.69	0.79	-1.44*	0.08
Sodium (mEq/L)				
Baseline Mean	141.18	139.82	140.85	140.16
Mean Change to Minimum	-2.77	-1.59	-1.92	-0.87*
Potassium (mEq/L)				
Baseline Mean	4.55	4.41	4.53	4.38
Mean Change to Minimum	-0.32	-0.15*	-0.19	-0.15*
Chloride (mEq/L)				
Baseline Mean	104.37	102.56	103.32	102.23
Mean Change to Minimum	-3.00	-1.15*	-1.95	-1.34*
Mean Change to Final	-0.71	0.80*	-1.00	0.29
Bicarbonate (mEq/L)				
Baseline Mean	26.42	26.72	27.10	27.57
Mean Change to Maximum	1.26	0.33*	0.71	0.61
Calcium (mg/dL)				
Baseline Mean	9.51	9.46	9.57	9.51
Mean Change to Minimum	-0.33	-0.17*	-0.21	-0.07*
Inorganic Phosphorus (mg/dL)				
Baseline Mean	3.64	3.71	3.72	3.56
Mean Change to Minimum	-0.42	-0.27	-0.11*	-0.11*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters (continued)

Blood Chemistry Parameter (units)	Treatment Group			
		ABT-594		
	Placebo (N=62)	150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Cholesterol (mg/dL)				
Baseline Mean	190.44	199.54	204.95	203.79
Mean Change to Maximum	12.71	4.44*	-1.05*	0.21*
Mean Change to Final	1.27	-3.66	-8.55*	-5.53
Triglycerides (mg/dL)				
Baseline Mean	239.31	274.03	277.55	300.03
Mean Change to Maximum	80.69	42.26	28.77*	-7.34*
Mean Change to Final	39.32	-9.11*	-3.59	-36.23*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Urinalysis

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for urinalysis is presented in Table 12.4c.

Table 12.4c Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Urinalysis Parameters

Urinalysis Parameter (units)	Treatment Group			
		ABT-594		
	Placebo (N=61)	150 µg BID (N=58)	225 µg BID (N=65)	300 µg BID (N=62)
Urine pH				
Baseline Mean	5.75	5.59	5.51	5.68
Mean Change to Minimum	-0.67	-0.36*	-0.26*	-0.19*
Mean Change to Final	-0.34	-0.12	-0.09	0.00*
Specific Gravity				
Baseline Mean	1.02	1.02	1.02	1.02
Mean Change to Minimum	-0.004	-0.003	-0.002	-0.001*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

12.4.2.2 Individual Subject Changes

The percentage of subjects with shifts in laboratory parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.4__2.1 for hematology variables, Table 14.3.4__2.2 for blood chemistry variables, and Table 14.3.4__2.3 for urinalysis variables. The majority of subjects had clinical laboratory values within normal range at the Baseline and Final Visits.

12.4.2.3 Individual Clinically Significant Abnormalities

Hematology Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant hematology values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.1. The percentages of subjects who had hematology values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed

hematology values that met the potentially clinically significant criteria are presented in Table 12.4d; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4d Number and Percentage of Subjects with Hematology Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
			ABT-594		
		Placebo	150 µg BID	225 µg BID	300 µg BID
Hemoglobin	High: ≥18.5 g/dL (males) ≥16.5 g/dL (females)	(N=54) 1 (2%)	(N=50) 0	(N=45) 0	(N=34) 0
Hematocrit	Low: ≤37% (males) ≤32% (females)	(N=49) 4 (8%)	(N=47) 3 (6%)	(N=42) 4 (10%)	(N=32) 0
RBC	Low: ≤3.8 x 10^{12}/L (males) ≤3.5 x 10^{12}/L (females)	(N=53) 0	(N=50) 0	(N=45) 1 (2%)	(N=34) 0
WBC	High: ≥16.0 x 10^{9}/L	(N=56) 0	(N=51) 0	(N=45) 0	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Individual subjects with hematology values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.1.

Blood Chemistry Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant blood chemistry values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.2. The percentages of subjects who had blood chemistry values that met the potentially clinically significant criteria were generally similar among the treatment groups. One subject (4246) in the ABT-594 300 µg BID treatment group had a very high glucose on Day 14 (334 mg/dL) and was prematurely discontinued from study drug due to hyperglycemia. However, the

subject's glucose was high (229 mg/dL) at baseline, indicating poor control of her diabetes. The percentages of subjects who developed blood chemistry values that met the potentially clinically significant criteria are presented in Table 12.4e; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4e Number and Percentage of Subjects with Blood Chemistry Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
			ABT-594		
		Placebo	150 µg BID	225 µg BID	300 µg BID
Glucose	High: ≥175 mg/dL	(N=33) 19 (58%)	(N=23) 16 (70%)	(N=28) 16 (57%)	(N=20) 7 (35%)
	Low: ≤45 mg/dL	0	1 (4%)	0	0
Uric Acid	High: ≥10.5 mg/dL (males) ≥8.5 mg/dL (females)	(N=56) 0	(N=51) 0	(N=42) 0	(N=34) 1 (3%)
BUN	High: ≥30 mg/dL	(N=56) 2 (4%)	(N=51) 1 (2%)	(N=43) 0	(N=34) 1 (3%)
Creatinine	High: ≥2.0 mg/dL	(N=57) 0	(N=51) 1 (2%)	(N=45) 0	(N=35) 0
Chloride	Low: ≤90 mEq/L	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Calcium	Low: ≤8.2 mg/dL	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Triglycerides	High: ≥600 mg/dL	(N=54) 2 (4%)	(N=43) 0	(N=40) 2 (5%)	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Individual subjects with blood chemistry values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.2.

Urinalysis Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant urinalysis values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.3. The percentages of subjects who had urinalysis values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed urinalysis values that met the potentially clinically significant criteria are presented in Table 12.4f; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4f Number and Percentage of Subjects with Urinalysis Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
			ABT-594		
		Placebo	150 µg BID	225 µg BID	300 µg BID
Urine Glucose	High: ≥3+ [a]	(N=50) 12 (24%)	(N=44) 12 (27%)	(N=41) 10 (24%)	(N=27) 5 (19%)
Urine Protein	High: ≥3+ [a] / ≥10	(N=56) 0	(N=50) 0	(N=45) 0	(N=32) 1 (3%)
Urine Ketones	High: ≥3+ [a]	(N=57) 1 (2%)	(N=50) 0	(N=45) 0	(N=32) 0
Urine RBCs	High: ≥8/hpf (male) ≥10/hpf (female)	(N=57) 2 (4%)	(N=50) 3 (6%)	(N=44) 0	(N=31) 2 (6%)
Urine WBCs	High: ≥10/hpf/≥ 2+	(N=55) 4 (7%)	(N=50) 2 (4%)	(N=45) 3 (7%)	(N=32) 4 (13%)

hpf = high power field.

[a] ≥3+ on a scale with 4+ being the maximum value.

Cross Reference: Table 14.3.4__4.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

Individual subjects with urinalysis values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.3.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Listing of Individual Measurements by Subject and Each Abnormal Value

The location of vital sign, physical findings, and safety data is presented below.

Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing Appendix
Physical Examination	None	None	16.2__4.4
Vital Signs	14.3.5__1	14.3.5__2	16.2__9.1
		14.3.5__3	
ECGs	14.3.6__1	14.3.6__3	16.2__9.2
	14.3.6__2	14.3.6__4	

No normal reference range was used for evaluating vital sign or ECG variables. Criteria for potentially clinically significant values (i.e., Very High or Very Low values) for vital signs and ECG are presented in Table 14.3.4__1.0.

12.5.2 Findings on Physical Examination

Clinically significant deteriorations from baseline physical examination were captured as adverse events (Appendices 16.2__4.4 and 16.2__7.1.1).

12.5.3 Vital Signs Evaluation

12.5.3.1 Vital Signs Values Over Time

Statistically significant differences were observed between treatment groups for mean change from baseline to minimum and/or maximum; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for vital sign parameters is presented in Table 12.5a.

Table 12.5a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Vital Sign Parameters

Vital Sign Parameter (units)	Treatment Group			
		ABT-594		
	Placebo (N=62)	150 µg BID (N=62)	225 µg BID (N=66)	300 µg BID (N=64)
Systolic Blood Pressure (mm Hg)				
Baseline Mean	130.8	134.3	136.8	133.9
Mean Change to Maximum	11.8	8.6	3.9*	7.6
Diastolic Blood Pressure (mm Hg)				
Baseline Mean	76.3	78.7	77.6	76.5
Mean Change to Maximum	6.4	4.5	2.7*	4.6
Mean Change to Final	1.4	-3.2*	-1.5	0.8
Heart Rate (bpm)	(N=62)	(N=61)	(N=66)	(N=63)
Baseline Mean	76.1	75.4	75.2	76.1
Mean Change to Final	2.5	-1.8*	2.0	0.6
Weight (pounds)	(N=61)	(N=60)	(N=62)	(N=60)
Baseline Mean	204.0	199.8	199.1	204.1
Mean Change to Minimum	-0.1	-2.1*	-1.9*	-2.8*
Mean Change to Maximum	1.8	0.0*	-0.1*	-1.4*
Mean Change to Final	1.1	-0.8*	-1.0*	-2.0*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.5__1 and Appendix 16.2__9.1

12.5.3.2 Individual Subject Changes

Criteria for potentially clinically significant vital signs and weight values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.5__3. The percentages of subjects who had vital signs values that met the potentially clinically significant criteria were generally similar among the treatment groups. A very high sitting systolic blood pressure value was reported by 0 placebo-treated subjects, 6% (3/50) of ABT-594 150 µg-treated subjects, 0 ABT-594 225 µg-treated subjects, and 3% (1/36) of ABT-594 300 µg BID-treated subjects (Table 14.3.5__3).

12.5.4 Electrocardiogram Evaluation

12.5.4.1 ECG Values Over Time

No statistically significant differences were observed between placebo and any of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value for ECG variables (Table 14.3.6__1).

12.5.4.2 Individual Clinically Significant Abnormalities

The percentage of subjects with shifts in ECG parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.6__2. The majority of subjects had ECG values within normal range at the Baseline and Final Visits.

12.5.4.3 Individual Clinically Significant Abnormalities

Criteria for potentially clinically significant ECG values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.6__4. The percentages of subjects who had ECG values that met the potentially clinically significant criteria were generally similar among the treatment groups. Of note, the high QT_C interval in an ABT-594 225 µg BID-treated subject (4081) was an isolated occurrence that was not associated with an adverse event. The percentages of subjects who developed ECG values that met the potentially clinically significant criteria are presented in Table 12.5b; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.5b Number and Percentage of Subjects with ECG Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
			ABT-594		
		Placebo	150 µg BID	225 µg BID	300 µg BID
QT_C Interval[a]	High: ≥500 msec	(N=49) 0	(N=41) 0	(N=30) 1 (3%)	(N=21) 0
PR Interval	High: ≥210 msec	(N=44) 1 (2%)	(N=41) 0	(N=30) 1 (3%)	(N=20) 0
Heart Rate	High: ≥120 bpm and increased ≥30 bpm from baseline	(N=50) 0	(N=41) 0	(N=31) 2 (6%)	(N=21) 0

a QT_C calculated as QT divided by the square root of RR interval.

Cross Reference: Table 14.3.6__4 and Appendix 16.2__9.2

Individual subjects with ECG values that met the potentially clinically significant criteria are summarized in Table 14.3.6__3.

12.6 Safety Conclusions

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and

300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

13.0 Discussion and Overall Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 μg, 225 μg, and 300 μg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 μg and 300 μg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 μg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 μg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 μg, 2 ABT-594 225 μg, and 4 ABT-594 300 μg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 μg, 1 ABT-594 225 μg, and 2 ABT-594 300 μg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 μg, 32 ABT-594 225 μg, and 44 ABT-594 300 μg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

PLs' HJ

May 25, 2000

Michael Hoffstetter, MD
Prince William Neuroscience Center
2296 Opitz Boulevard, Suite 400
Woodbridge, VA 22191

RE: M99-114, A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr. Hoffstetter:

The M99-114 study has its share of enrollment challenges and Abbott appreciates the difficulties some sites have encountered in finding subjects who meet our stringent inclusion/exclusion criteria. Your site has been up and running for approximately one month and during this time you have not been able to screen any subjects. Unfortunately, we find it necessary to discontinue the M99-114 clinical trial at your site This action is needed for two reasons: 1) to avoid the statistical bias that can be caused when too few patients are enrolled at a single site and 2) to increase our probability of meeting enrollment goals by bringing on additional back-up sites. As of today, please do not screen or randomize any additional patients.

We intend to compensate you for your time and effort to date. Your RSI monitor will be in contact to set up a close-out visit.

We sincerely apologize for any difficulties this may cause and hope we can work together again in the future. If you have any questions, please don't hesitate to contact me. I can be reached at 847-938-1199 (phone), 847-938-5258 (fax), or marilyn.collicott@abbott.com (email).

Thank you so much for your efforts in the M99-114 study.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture